

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

THIS PAGE BLANK (USPTO)

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | | |
|--|--|--|--|
| <p>(51) International Patent Classification⁵ : C07D 239/48, 239/50, 239/42 A61K 31/505, C07D 239/95 C07D 495/04, 239/70</p> | | A1 | <p>(11) International Publication Number: WO 91/18887 (43) International Publication Date: 12 December 1991 (12.12.91)</p> |
| <p>(21) International Application Number: PCT/EP91/01007 (22) International Filing Date: 1 June 1991 (01.06.91)</p> | | <p>(74) Agent: GIDDINGS, Peter, John; Corporate Patents, SmithKline Beecham, Mundells, Welwyn Garden City, Hertfordshire AL7 1EY (GB).</p> | |
| <p>(30) Priority data: 9012592.3 6 June 1990 (06.06.90) GB</p> | | <p>(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent), US.</p> | |
| <p>(71) Applicant (for all designated States except US): SMITH-KLINE BEECHAM INTERCREDIT B.V. [NL/NL]; 28-34 Blaak, P.O. Box 2, NL-3000 DG Rotterdam (NL).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only) : IFE, Robert, John [GB/GB]; BROWN, Thomas, Henry [GB/GB]; LEACH, Colin, Andrew [GB/GB]; SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB).</p> | | <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p> | |
| <p>(54) Title: DIAMINOPYRIMIDINE COMPOUNDS</p> | | | |
| <p>(57) Abstract Diaminopyrimidine compounds and their use as inhibitors of gastric acid secretion.</p> | | | |

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | |
|----|--------------------------|----|--|----|--------------------------|
| AT | Austria | ES | Spain | MG | Madagascar |
| AU | Australia | FI | Finland | ML | Mali |
| BB | Barbados | FR | France | MN | Mongolia |
| BE | Belgium | GA | Gabon | MR | Mauritania |
| BF | Burkina Faso | GB | United Kingdom | MW | Malawi |
| BG | Bulgaria | GN | Guinea | NL | Netherlands |
| BJ | Benin | GR | Greece | NO | Norway |
| BR | Brazil | HU | Hungary | PL | Poland |
| CA | Canada | IT | Italy | RO | Romania |
| CF | Central African Republic | JP | Japan | SD | Sudan |
| CG | Congo | KP | Democratic People's Republic of Korea | SE | Sweden |
| CH | Switzerland | KR | Republic of Korea | SN | Senegal |
| CI | Côte d'Ivoire | LI | Liechtenstein | SU | Soviet Union |
| CM | Cameroon | LK | Sri Lanka | TD | Chad |
| CS | Czechoslovakia | LU | Luxembourg | TG | Togo |
| DE | Germany | MC | Monaco | US | United States of America |
| DK | Denmark | | | | |

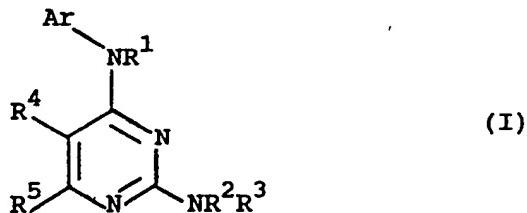
- 1 -

DIAMINOPYRIMIDINE COMPOUNDS

5 The present invention relates to substituted
 2,4-diaminopyrimidine derivatives, processes for their
 preparation, intermediates useful in their preparation,
 pharmaceutical compositions containing them and their
 use in therapy.

10 Accordingly the present invention provides, in a
 first aspect compounds of structure (I)

15



20 in which

Ar is a phenyl ring which can be optionally substituted by
 one to three groups selected from hydroxy, halogen,
 CF_3 , C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, cyano,
 25 amino, carbamoyl, carboxy or C_{1-4} alkanoyl;

R^1 is hydrogen or C_{1-4} alkyl;

30 R^2 and R^3 are the same or different and are each hydrogen,
 C_{1-4} alkyl or Ar^1 where Ar^1 is as defined for Ar; or
 R^2 and R^3 together with the nitrogen atom to which
 they are attached form a saturated or unsaturated
 ring optionally containing one or more further
 heteroatoms.

35

- 2 -

one of R⁴ and R⁵ is hydrogen or C₁₋₄alkyl; and the other
is hydrogen, C₁₋₄alkyl, hydroxyC₁₋₄alkyl, C₁₋₄alkoxy-
C₁₋₄alkyl, amino, C₁₋₄alkanoyl, C₁₋₄alkylthioC₁₋₄alkyl,
Ar²(CH₂)_nOC₁₋₄alkyl, in which Ar² is an optionally
5 substituted phenyl ring as defined for Ar and n is 0
to 4; or -(CH₂)_mAr³, in which m is 1 to 4 and Ar³
is an optionally substituted phenyl ring as defined for
Ar; or R⁴ and R⁵ together with the carbon atoms to
which they are attached form a 5- or 6-membered ring,
10 optionally containing one or more heteroatoms;

and pharmaceutically acceptable salts thereof.

Suitably, Ar is an unsubstituted phenyl ring or a
15 phenyl ring substituted by 1 to 3 substituents selected
from hydrogen, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkylthio,
halogen, cyano, amino, hydroxy, carbamoyl, carboxy,
C₁₋₄alkanoyl or trifluoromethyl. More suitably, Ar is
an unsubstituted phenyl ring or one substituted by two
20 substituents selected from hydrogen, C₁₋₄alkyl,
C₁₋₄alkoxy, C₁₋₄alkylthio, halogen, cyano, amino,
hydroxy, carbamoyl, carboxy, C₁₋₄alkanoyl or trifluoro-
methyl. More preferably, Ar is an unsubstituted phenyl
ring or one substituted by two substituents selected from
25 C₁₋₄alkyl and C₁₋₄alkoxy. Most preferably, Ar is an
unsubstituted phenyl ring or one substituted by a single
substituent selected from the above-noted groups, in
particular hydroxy, halogen, C₁₋₄alkyl or C₁₋₄alkoxy.

30 Suitably R¹ is hydrogen or C₁₋₄alkyl; preferably
R¹ is C₁₋₄alkyl. Most preferably R¹ is methyl.

Suitably R² and R³ are the same or different and
are each hydrogen, C₁₋₄alkyl or a ring Ar¹ or R² and

- 3 -

R³ together with the nitrogen atom to which they are attached form a saturated or unsaturated ring optionally containing one or more further heteroatoms. More suitably one of R² and R³ is hydrogen or C₁₋₄alkyl and the other is hydrogen, C₁₋₄alkyl or a ring Ar¹ or R² and R³ together with the nitrogen atom to which they are attached form a saturated or unsaturated ring optionally containing one or more further heteroatoms. Most suitably, one of R² and R³ is hydrogen or C₁₋₄alkyl and the other is hydrogen, C₁₋₄alkyl or any Ar¹. Preferably one of R² and R³ is hydrogen or C₁₋₄alkyl and the other is a ring Ar¹; more preferably one of R² and R³ is hydrogen and the other is a ring Ar¹.

Suitably Ar¹ is an unsubstituted phenyl ring or a phenyl ring substituted as defined for Ar. Preferably Ar¹ is an unsubstituted phenyl ring or a phenyl ring substituted by 1 or 2 substituents selected from C₁₋₄alkyl and halogen.

Suitably, one of R⁴ and R⁵ is hydrogen or C₁₋₄alkyl, and the other is hydrogen, C₁₋₄alkyl, hydroxyC₁₋₄alkyl, C₁₋₄alkoxyC₁₋₄alkyl, amino, C₁₋₄alkanoyl, C₁₋₄alkylthio-C₁₋₄alkyl, Ar²(CH₂)_nOC₁₋₄alkyl, in which Ar² is an optionally substituted phenyl ring as described for Ar and n is 0 to 4, or -(CH₂)_mAr³ in which Ar³ is an optionally substituted phenyl ring as described for Ar and m is 1 to 4; or R⁴ and R⁵ together with the carbon atoms to which they are attached form a 5- or 6-membered ring optionally containing one or more heteroatoms. Preferably R⁴ is hydrogen or C₁₋₄alkyl and R⁵ is C₁₋₄alkyl, hydroxyC₁₋₄alkyl or C₁₋₄alkoxyalkyl; or R⁴ and R⁵ together with the carbon atoms to which they are attached form a 6-membered carbocyclic ring.

- 4 -

Suitably Ar² is an optionally substituted phenyl ring as described for Ar; preferably Ar² is an unsubstituted phenyl ring. Suitably n is 0 to 4, preferably n is 1.

5

Suitably Ar³ is an optionally substituted phenyl ring as described for Ar; preferably Ar³ is an unsubstituted phenyl ring. Suitably m is 1 to 4, preferably m is 1.

10

Suitable rings formed by R⁴ and R⁵ together with the carbon atoms to which they are attached, containing one or more heteroatoms include, for example, 5- or 6-membered rings containing a sulphur, oxygen or nitrogen atom and, in addition, 5- or 6-membered rings containing a sulphur atom in which the sulphur atom is in the form of the sulphoxide or sulphone, as hereinafter described in the examples.

20

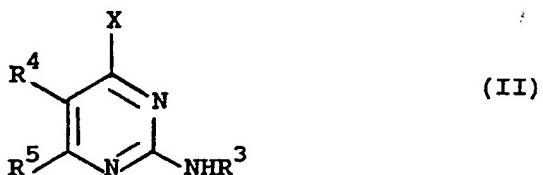
C₁₋₄alkyl groups (either alone or as part of another group) can be straight or branched.

It will be appreciated that compounds of structure (I) in which one or more of R¹ to R⁵ is a C₃₋₄alkyl group (either alone or as part of another group) may contain an assymmetric centre due to the presence of the C₃₋₄alkyl group. Such compounds will exist as two (or more) optical isomers (enantiomers). Both the pure enantiomers, racemic mixtures (50% of each enantiomer) and unequal mixtures of the two are included within the scope of the present invention. Further, all diastereomeric forms possible (pure enantiomers and mixtures thereof) are within the scope of the invention.

- 5 -

The compounds of the present invention can be prepared by processes analogous to those known in the art. The present invention therefore provides in a further aspect a process for the preparation of a compound of structure (I) or a pharmaceutically acceptable salt thereof which comprises reaction of a compound of structure (II)

10



15 in which R³ to R⁵ are as described for structure (I), and X is a group displaceable by an amine, with an amine of structure ArNR¹H in which Ar and R¹ are as described for structure (I), and optionally thereafter, forming a pharmaceutically acceptable salt.

20

Suitable groups displaceable by an amine X will be apparent to those skilled in the art and include, for example, halogen in particular chlorine, SC₁₋₄alkyl such as methylthio and phenoxy.

25

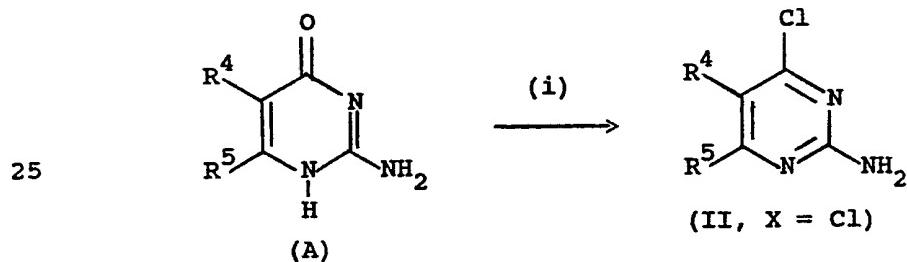
Reaction of a compound of structure (II) with an amine ArR¹NH is suitably carried out in an inert solvent at elevated temperature. Preferably the reaction is carried out in the absence of a solvent in a sealed receptacle at 30 elevated temperature. Most preferably in an inert solvent for example dioxan, at reflux temperature.

- 6 -

Pharmaceutically acceptable acid addition salts of the compounds of structure (I) can be prepared by standard procedures by, for example, reaction with suitable organic and inorganic acids the nature of which will be apparent to persons skilled in the art. For example, pharmaceutically acceptable salts can be formed by reaction with hydrochloric, sulphuric, or phosphoric acids; aliphatic, aromatic or heterocyclic sulphonic acids or carboxylic acids such as, for example, citric, maleic or fumaric acids, or methyl sulphonic acid.

The intermediate compounds of structure (II) can be prepared by procedures analogous to those known in the art. The amines of structure ArR^1NH are available commercially or can be prepared by standard techniques well known to those skilled in the art of organic chemistry.

For example, compounds of structure (II) in which R^2 and R^3 are hydrogen can be prepared by the following procedure :



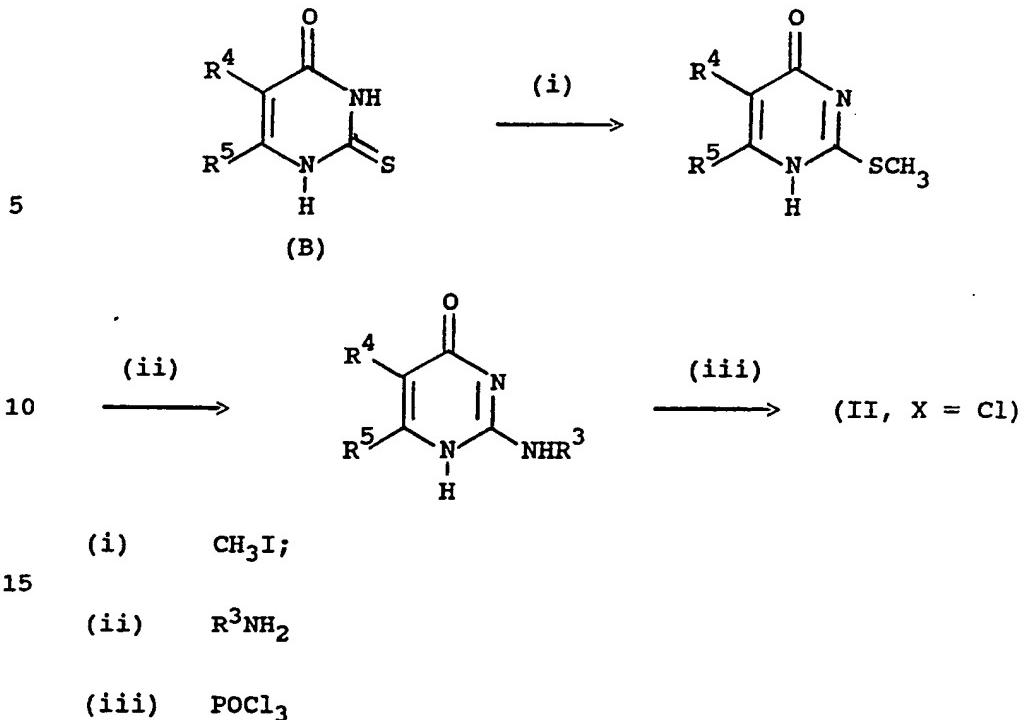
(i) POCl_3 .

30

The starting materials (A) are known or can be prepared by standard procedures.

35 Compounds of structure (II) in which R^3 is other than hydrogen can be prepared by the following procedures :

- 7 -



20 Compounds (B) are known or can be prepared by standard techniques.

The compounds of structure (I) and their pharmaceutically acceptable salts exert an anti-secretory effect by inhibition of the gastrointestinal H^+K^+ ATPase enzyme.

In a further aspect therefore the present invention provides compounds of structure (I) and pharmaceutically acceptable salts thereof for use in therapy.

The compounds of structure (I) and their pharmaceutically acceptable salts inhibit exogenously and endogenously stimulated gastric acid secretion and are

- 8 -

useful in the treatment of gastrointestinal diseases in mammals, in particular humans. Such diseases include, for example, gastric and duodenal ulcers, and Zollinger-Ellison Syndrome. Further, the compounds of structure (I) can be used in the treatment of other disorders where an anti-secretory effect is desirable for example in patients with gastritis, NSAID induced gastritis, gastric ulcers, acute upper intestinal bleeding, in patients with a history of chronic and excessive alcohol consumption, and in patients with gastro oesophageal reflux disease (GERD).

In therapeutic use, the compounds of the present invention are usually administered in a standard pharmaceutical composition.

The present invention therefore provides in a further aspect pharmaceutical compositions comprising a compound of structure (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The compounds of structure (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as liquids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavouring or colouring agent.

- 9 -

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, 5 sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be 10 prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, 15 celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or 20 parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior 25 to administration.

A typical suppository formulation comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent such as 30 polymeric glycals, gelatins or cocoa butter or other low melting vegetable or synthetic waxes or fats.

Preferably the composition is in unit dose form such as a tablet or capsule.

- 10 -

Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

The pharmaceutically acceptable compounds of the invention will normally be administered in a daily dosage regimen (for an adult patient) of, for example, an oral dose of between 1 mg and 500 mg, preferably between 1 mg and 250 mg, or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 25 mg, of the compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

In addition, the compounds of the present invention can be co-administered with further active ingredients in particular when used to treat conditions caused or exacerbated by gastric acidity. Such ingredients include antacids (for example magnesium carbonate or hydroxide and aluminium hydroxide), non-steroidal anti-inflammatory drugs (for example indomethacin, aspirin or naproxen), steroids, or nitrite scavengers (for example ascorbic acid or aminosulphonic acid), or other drugs used for treating gastric ulcers (for example pirenzipine, prostaglandins for example 16,16 dimethyl PGE₂, or histamine H₂-antagonists (for example, cimetidine)).

The present invention also provides in a still further aspect, a method of treatment of gastrointestinal diseases caused or exacerbated by gastric acid in mammals,

- 11 -

including man which comprises administering to a subject in need thereof an effective amount of a compound of structure (I) or a pharmaceutically acceptable salt thereof.

5

The following examples illustrate the invention.
Temperatures are recorded in degrees centigrade.

- 12 -

Example 1

2-Amino-4-methyl-6-[(2-methylphenyl)amino]pyrimidine hydrochloride

5

2-Amino-4-chloro-6-methylpyrimidine (2.0 g, 0.014 m) and o-toluidine (4.0 g - excess) were mixed at room temperature and heated with stirring under nitrogen in an oil-bath. The oil-bath temperature was raised to 165°, held thus for two hours and the reactants then cooled to room temperature. Acetone was added to the resulting oil and on scratching a crystalline solid separated. After standing at ~0° overnight the solid was collected washed with acetone and dried (3.47 g, pale-pink solid). This solid was re-crystallised from absolute ethanol/diethyl ether to give the title compound as its hydrochloride salt (2.64 g), m.p. = 229-231°.



Found: C 57.7, H 6.1, N 22.3, Cl⁻ 14.0
20 Requires: C 57.5, H 6.0, N 22.4, Cl⁻ 14.1

Example 2

2-Amino-4,5-dimethyl-6-[(2-methylphenyl)amino]pyrimidine hydrochloride

Substituting 2-amino-4-chloro-5,6-dimethyl-pyrimidine (2.1 g, 0.0133 m) for 2-amino-4-chloro-6-methylpyrimidine and using corresponding molar proportions of the other 30 reagents in Example 1 produced a solid (3.16 g). This solid was re-crystallised from isopropanol to give the

- 13 -

title compound (2.63 g) as its hydrochloride salt,
m.p. = 305-306°



Found: C 58.8, H 6.4, N 21.1, Cl⁻ 13.2
Requires: C 59.0, H 6.5, N 21.2, Cl⁻ 13.4

Example 3

2-Amino-4-[(2-methylphenyl)amino]pyrimidine

10

2-Amino-4-chloropyrimidine (2.2 g, 0.01698 m) and o-toluidine (4.0 g, excess) were mixed at room temperature and heated with stirring (under an air condenser) in an oil-bath at 165-170° for two hours. After cooling the 15 violet oil was taken up in a small volume of water and 2N HCl added dropwise with stirring to give a suspension at pH 4.5. This was extracted with chloroform (4 x 200 ml) to remove o-toluidine. The aqueous solution remaining was basified with NaOH (→ pH 8.5) and again extracted 20 with chloroform (4 x 200 ml). The latter chloroform extracts were combined, dried (K₂CO₃) and evaporated to dryness to give a glass which crystallised on standing. This material was re-crystallised from ethanol/water to give the title compound (1.64 g) as a 25 very pale-pink solid, m.p. = 118-120°.



Found: C 65.8, H 6.0, N 27.9
Requires: C 66.0, H 6.0, N 28.0

30

Example 4

2-Amino-4-methyl-6-(N-methylphenylamino)pyrimidine
hydrochloride

35 Substituting N-methylaniline (4.0 g - excess) for

- 14 -

o-toluidine and using corresponding molar proportions of the other reagents in Example 1 gave a white solid (2.0 g). This was re-crystallised from ethanol/ether to give the title compound (1.21 g) as its hydrochloride salt,
5 m.p. = 243-245°.



Found: C 57.4, H 5.9, N 22.6

Requires: C 57.5, H 6.0, N 22.4

10

Example 5

2,4-Bis-[(2-methylphenyl)amino]-6-methylpyrimidine hydrochloride

15 2,4-Dichloro-6-methylpyrimidine (1.63 g, 0.01 m) and o-toluidine (4.28 g, 0.04 m) were mixed at room temperature and heated with stirring in an oil-bath at ~150° for two hours. The cooled reaction mixture was treated with acetone to give a white solid in a pinky-red solution. The
20 solid was collected, washed with acetone and dried to give the title compound (2.65 g) as its hydrochloride salt,
m.p. = 216-218°.



Found: C 67.2, H 6.2, N 16.6, Cl⁻ 10.0

25 Requires: C 67.0, H 6.2, N 16.4, Cl⁻ 10.4

Example 6

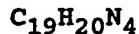
2,4-Bis-(N-methylphenylamino)-6-methylpyrimidine

30

2,4-Dichloro-6-methylpyrimidine (1.63 g, 0.01 m) and N-methylaniline (2.14 g, 0.02 m) were mixed at room temperature and heated with stirring in an oil-bath at

- 15 -

~150° for two hours. The resulting pale-yellow oil was dissolved in water and the aqueous solution basified with saturated aqueous Na₂CO₃ solution. The mixture was extracted with ether and the ethereal solution washed with water and brine, dried and evaporated to dryness to give an oil. This oil was chromatographed on silica gel using methylene chloride as eluting solvent. Fractions were monitored by t.l.c. and appropriate fractions combined and evaporated to give a white solid which was triturated with 40-60 petroleum ether, filtered and dried to give the title compound (0.63 g), m.p. = 63-65°.



Found: C 75.0, H 6.7, N 18.2

Requires: C 75.0, H 6.6, N 18.4

15

Example 7

2-(N-Methylphenylamino)-4-[(2-methylphenyl)amino]-6-methylpyrimidine hydrochloride

20

(i) 4-Chloro-6-methyl-2-(N-methylphenylamino)pyrimidine

6-Methyl-2-(N-methylphenylamino)pyrimidin-4-one (J. Het. Chem. (1984), 21, 1161) (4.6 g, 0.0214 m) and phosphorous oxychloride (20 ml) were mixed at room temperature and heated together at reflux temperature for two hours. The dark-brown solution was cooled and poured onto ice to produce, after decomposition of excess reagent, a yellow acidic solution. This was basified (→ pH 8) with 6N. NaOH and the aqueous mixture extracted with ethyl acetate. The brown organic solution was washed with water, dried and evaporated to give the title compound as a brown oil, 3.06 gms (Mass spectrum M-H = 232).

- 16 -

(ii) 2-(N-methylphenylamino)-4-[(2-methylphenylamino)-6-methylpyrimidine hydrochloride.

4-Chloro-6-methyl-2-(N-methylphenylamino) pyrimidine
5 (3.0 g, oil, 0.0129 m) and o-toluidine (1.38 g, 0.0129 m)
were mixed at room temperature and heated in an oil-bath,
with stirring, to 140°. After twenty minutes at this
temperature the mixture completely solidified. After
cooling acetone was added and the solid collected, ground
10 to a powder, washed with more acetone and dried (3.85 g).
This solid was re-crystallised from ethanol/ether to give
the title compound (2.48 g) as its hydrochloride salt,
light-buff, m.p. = 238-240°.



15 Found: C 66.9, H 5.9, N 16.4, Cl⁻ 10.2
Requires: C 67.0, H 6.2, N 16.4, Cl⁻ 10.4

Example 8

20 2-[(2-Methylphenyl)amino]-4-(N-methylphenylamino)-6-methylpyrimidine hydrochloride

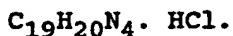
(i) 4-Chloro-6-methyl-2-[(2-methylphenyl)amino]pyrimidine

25 Substituting 6-methyl-2-[(2-methylphenyl)amino]-pyrimidin-4-one (J.C.S. (1946), 351) (3.63 g, 0.0159 m)
for 6-methyl-2-(N-methylphenylamino)pyrimidin-4-one
and using corresponding molar proportions of the other
reagents in Example 7(i) gave the title compound as an
30 oil (3.94 g), which crystallised on standing under
vacuum overnight.

(ii) 2-[(2-Methylphenyl)amino]-4-(N-methylphenylamino)-6-methylpyrimidine hydrochloride.

- 17 -

4-Chloro-6-methyl-2-[(2-methylphenyl)amino]pyrimidine (3.9 g, 0.01674 m) and N-methylaniline (1.79 g, 0.01674 m) were mixed at room temperature and heated with stirring in an oil-bath at 140° for three hours. The red-oil produced
5 was cooled to ~50° and acetone added to give, on scratching a light buff solid which was collected, washed with acetone and dried (3.56 g). This solid was re-crystallised from ethanol/ether to give the title compound (3.01 g) as light-buff needles, m.p. = 203-205°
10 (hydrochloride salt).



Found: C 66.9, H 6.3, N 16.5, Cl⁻ 10.3

Requires: C 67.0, H 6.2, N 16.4, Cl⁻ 10.4

15

Example 9

2-[(2-Methylphenyl)amino]-4-(phenylamino)-6-methyl-pyrimidine hydrochloride

20 Substituting aniline (0.718 g, 0.00644 m) for N-methylaniline and using corresponding molar proportions of the other reagents in Example 8(ii), gave a buff-coloured solid (1.33 g). This was re-crystallised from ethanol/diethyl ether to give the title compound (1.04 g)
25 as its hydrochloride salt (pale-buff), m.p. = 212-214°.



Found: C 65.9, H 5.9, N 17.0

Requires: C 66.2, H 5.9, N 17.1

30

Example 10

2-[(2-Methylphenyl)amino]-4-(N-methyl-2-methylphenylamino)-6-methylpyrimidine hydrochloride

35 Substituting N-methyl-o-toluidine (0.935 g, 0.00772 m)

- 18 -

for N-methylaniline and using corresponding molar proportions of the other reagents in Example 8(ii), gave after addition of acetone, a red solution (no solid crystallised at this stage). Diethyl ether was added to 5 this solution and after standing overnight in the fridge a solid separated and was collected, washed with acetone/diethyl ether and dried to give a light-grey powder (0.7 g). This was crystallised from acetone/diethyl ether to give the title compound (0.35 g) as its hydrochloride salt, m.p. = 179-180°.



Found: C 67.3, H 6.5, N 15.2

Requires: C 67.7, H 6.5, N 15.8

15

Example 11

2-Amino-4-[(2-methylphenyl)amino]-6-n-propyl pyrimidine.

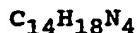
20 (i) 2-Amino-4-chloro-6-n-propylpyrimidine

2-Amino-6-n-propylpyrimidin-4-one (J.C.S.(C), (1968), 2358-67) (6.7 g, 0.0437 m) and phosphorus oxychloride (40 ml) were mixed at room temperature and heated at 25 reflux temperature for three hours to produce an orange solution. This was cooled, poured onto ice and stirred for several hours. The aqueous medium was neutralised with 6N. NaOH and again stirred in ice. A brown solid precipitate resulted which was extracted into ethyl acetate. The organic extracts were combined, washed, dried and evaporated to give a buff solid which was immediately used in the next stage of the synthesis 30 (Mass spectrum → M/e = 171).

- 19 -

(ii) 2-Amino-4-[(2-methylphenyl)amino]-6-n-propyl
pyrimidine

2-Amino-4-chloro-6-n-propylpyrimidine (1.65,
5 0.00965 m) and o-toluidine (4.0 g - excess) were mixed at
room temperature and heated with stirring in an oil-bath
at 140° for four hours. After cooling acetone was added
to give a purply-red solution. Diethylether was added to
precipitate a purple oil. The solution was decanted off
10 and the residual oil triturated several times with
diethylether. The oil was dissolved in acetone, water
added and the purple solution basified with aqueous
 Na_2CO_3 when a solid precipitated which was collected,
washed with water and dried (2.25 g). This material was
15 crystallised from acetone/water to give the title compound
(1.55) as buff needles, m.p. = 151-153°.



Found: C 69.4, H 7.5, N 23.3

Requires: C 69.4, H 7.5, N 23.1

20

Example 12

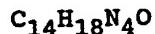
2-Amino-4-(2-methyl-4-hydroxyphenylamino)-6-n-propyl-
pyrimidine

25

Substituting 4-amino-m-cresol (4.0 gms, XS) for
o-toluidine and using corresponding molar proportions
of the other reagents in Example 11(ii) gave a dark-red
solution after addition of acetone to the reaction
30 mixture. Water was added followed by aqueous Na_2CO_3 to
basify the solution and precipitate a black solid which
was filtered off and discarded. The aqueous filtrate
was extracted with ethyl acetate and the combined organic
extracts back-washed with water. The ethyl acetate was

- 20 -

dried and evaporated to yield a dark-brown glass which solidified on treatment with diethyl ether and was collected, washed with ether and dried to a buff powder (2.72 g). This was charcoated in ethanol, concentrated and stood at 0° to give the title compound (1.14 g) as a buff-coloured crystalline solid, m.p. = 199-200°.



Found: C 64.8, H 6.9, N 21.7

Requires: C 65.1, H 7.0, N 21.7

10

Example 13

2-[(2-Methylphenyl)amino]-4-(N-methylphenylamino)-6-n-propylpyrimidine hydrochloride

15

(i) 2-[(2-Methylphenyl)amino]-6-propylpyrimidin-4-one

2-Methylthio-6-propylpyrimidin-4-one (Eur.J.Med. Chem., 1988, 23, 53) (9.21 g, 0.05 m) and o-toluidine (5.5 g, 0.052 m) were mixed at room temperature and heated with stirring in an oil-bath at 170° for five hours. Effluent gases were passed through a CHLOROS trap. The reaction mixture was cooled to produce a solid. Cold methanol was added and the insoluble solid collected, washed with cold methanol and dried to a light-grey solid (6.14 g) which was used immediately.

(ii) 4-Chloro-6-n-propyl-2-[(2-methylphenyl)amino]-pyrimidine

30

The product from Example 13 i) above (5.5 g, 0.0226 m) and phosphorous oxychloride (30 ml) were mixed at room temperature and heated at reflux temperature for

- 21 -

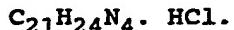
2% hours. The cooled solution was poured onto ice and the aqueous mixture neutralised with 6N. NaOH. The mixture was extracted with ethyl acetate, the organic extracts washed with water, dried and evaporated to give 5 a brown oil which crystallised on scratching (5.5 g) and was used immediately.

(iii) 2-[(2-Methylphenyl)amino]-4-(N-methylphenylamino)-6-n-propylpyrimidine hydrochloride.

10

The product from Example 13 ii) above (2.62 g, 0.01 m) and N-methylaniline (1.07 g, 0.01 m) were mixed at room temperature and heated, with stirring, in an oil-bath at 140° for two hours. The mixture, initially an oil, had 15 virtually solidified by this time and was cooled, acetone added and the insoluble solid collected (2.12 g). This was crystallised from ethanol/diethyl ether to give the title compound (1.53 g) as its blue-white hydrochloride salt, m.p. = 170-172°.

20



Found: C 68.2, H 6.8, N 15.1, Cl⁻ 9.6

Theory: C 68.4, H 6.8, N 15.2, Cl⁻ 9.6

Example 14

25

2-[(4-Fluoro-2-methylphenyl)amino]-4-(N-methylphenyl-amino)-6-n-propylpyrimidine hydrochloride

(i) 2-[(4-Fluoro-2-methylphenyl)amino]-6-n-propyl 30 pyrimidin-4-one.

Substituting 4-fluoro-2-methylaniline (4.0 g, 0.032 M) for o-toluidine and using corresponding molar

- 22 -

proportions of the other reagents in Example 13(i) gave a crystalline solid which was collected, washed with cold methanol and dried, to give a grey solid (5.36 g).

- 5 (ii) 4-Chloro-6-n-propyl-2-[(4-fluoro-2-methylphenyl)-amino]pyrimidine.

Substituting the product of Example 14(i) above (5.2 g, 0.0199 m) for 2-[(2-methylphenyl)amino]-6-n-propylpyrimidin-4-one and using corresponding molar proportions of the other reagents in Example 13(ii) gave a brown oil which crystallised on standing (3.4 gms) which was used immediately.

- 15 (iii) 2-[(4-Fluoro-2-methylphenyl)amino]-4-(N-methyl-phenylamino)-6-n-propylpyrimidine hydrochloride

4-Chloro-6-n-propyl-2-[(4-fluoro-2-methylphenyl)-amino]pyrimidine (3.0 g, 0.0107 m) and N-methylaniline (2.0 g, XS) were mixed at room temperature and heated, with stirring, in an oil-bath at 146° for 2½ hours. The brown oil produced was cooled, acetone added and, on standing at 0° overnight, crystals separated which were collected, washed with acetone and dried (1.56 g). This solid was re-crystallised from ethanol/diethyl ether to give the title compound (0.92 g) as its colourless hydrochloride salt, m.p. = 165-167°.



- Found: C 65.1, H 6.3, N 14.5, Cl⁻ 9.1
30 Requires: C 65.2, H 6.3, N 14.5, Cl⁻ 9.2

- 23 -

Example 15

2-[(4-Fluoro-2-methylphenyl)amino]-4-(N-methyl-2-methyl-phenylamino)-6-n-propylpyrimidine hydrochloride

5

Substituting N-methyl-o-toluidine (0.664 g, 0.00549 m) for N-methylaniline and using corresponding molar proportions of the other reagents in Example 14(iii) gave a red acetone solution after the heated reaction mixture had been allowed to cool. (N.B. In this example some white crystalline solid sublimed out of the heated reaction vessel during the reaction - this was shown by t.l.c. to be starting amine hydrochloride). The red acetone solution was evaporated to dryness and the residual oil dissolved in ethyl acetate. The red ethyl acetate solution was washed with aqueous Na_2CO_3 , H_2O , 2N.HCl and water, dried and evaporated to a buff solid (0.63 g). This was crystallised from ethanol/ diethylether to give the title compound (0.42 g) as its pale-buff hydrochloride salt, m.p. = 170-172°.



Found: C 65.5, H 6.4, N 13.8

Requires: C 65.9, H 6.5, N 14.0

25

Example 16

2-Amino-4-benzyl-6-[(2-methylphenyl)amino]pyrimidine

30

(i) 2-Amino-4-benzyl-6-chloropyrimidine.

2-Amino-6-benzylpyrimidin-4-one (J.Pharm.Sci. (1964), 53, 1317) (6.2 g, 0.0308 m) and phosphoryl chloride (40 ml)

- 24 -

were mixed at room temperature and heated under reflux for three hours. The mixture was cooled, poured onto ice and the aqueous mixture basified with 2N.NaOH and extracted with chloroform. The chloroform extracts were combined, 5 washed with water and brine, dried and evaporated to a green oily solid (2.25 g) which was used immediately.

(ii) 2-Amino-4-benzyl-6-[(2-methylphenyl)amino]pyrimidine

10 The product from Example 16(i) above (2.2 g, 0.01023 m) and o-toluidine (4.0 g, XS) were mixed at room temperature and heated with stirring in an oil-bath at 150° for three hours. The mixture was cooled, dissolved in methanol and acidified with 2N.HCl. The whole mixture 15 was evaporated to dryness and the residue dissolved in distilled water (a little insoluble material was filtered off and discarded). The clear aqueous solution was basified with 2N NaOH to precipitate a light-buff solid (1.2 g). This was crystallised, first from acetone and 20 finally from methanol/acetone to give the title compound (0.5 g), m.p. = 197-199°.



Found: C 74.5, H 6.1, N 19.3

Requires: C 74.5, H 6.3, N 19.3

25

Example 17

6-Benzyl-2-[(2-methylphenyl)amino]-4-(N-methylphenylamino)-
pyrimidine hydrochloride

30

(i) 6-Benzyl-2-[(2-methylphenyl)amino]pyrimidin-4-one

6-Benzyl-2-methylthiopyrimidin-4-one (Eur.J.Med.Chem. (1988), 23, 53) (8.37 g, 0.03608 m) and o-toluidine

- 25 -

(4.06 g, 0.038 m) were mixed at room temperature and heated with stirring in an oil-bath at 170° for six hours, effluent gases being passed through a CHLOROS trap. The mixture was then cooled and treated at room temperature 5 overnight with a mixture of methanol/acetone, 1:1. A yellow solid was produced which was collected, washed with acetone and dried (6.1 g). A portion was re-crystallised from methanol to give the title compound as an off-white solid, m.p. = 153-155°.

10 $C_{18}H_{17}N_3O$

Found: C 74.4, H 5.8, N 14.3

Requires: C 74.2, H 5.9, N 14.4

15 (ii) 4-Benzyl-6-chloro-2-[(2-methylphenyl)amino]pyrimidine

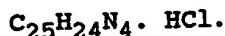
15 The product of Example 17(i) above (5.3 g, 0.0182 m) and phosphoryl chloride (30 ml) were mixed at room temperature and heated under reflux for 2½ hours. The orange solution was then cooled, poured onto ice and the 20 aqueous mixture neutralised with 40% NaOH. The mixture was extracted with ethyl acetate and the combined organic extracts washed, dried and evaporated to a yellow oil (5.1 g) which was used immediately without further purification.

25 (iii) 6-Benzyl-2-[(2-methylphenyl)amino]-4-(N-methyl-phenylamino)pyrimidine hydrochloride

30 The product from Example 17(ii) above (5.1 g, 0.0165 m) and N-methylaniline (3.53 g, 0.033 m) were mixed at room temperature and heated with stirring in an oil-bath at 150° for 2½ hours. The mixture was cooled and acetone added at ~70°. The mixture was boiled to give a clear

- 26 -

solution and cooled when a solid crystallised which was collected, washed with acetone and dried. The material was re-crystallised twice from ethanol/diethyl ether to give the title compound (2.18 g) as its blue-white hydrochloride
5 salt, m.p. = 183-185°.



Found: C 71.8, H 6.1, N 13.3, Cl⁻ 8.3

Requires: C 72.0, H 6.0, N 13.4, Cl⁻ 8.5

10

Example 18

5,6-Dimethyl-2-[(2-methylphenyl)amino]-4-(phenylamino)-pyrimidine hydrochloride

15 (i) 5,6-Dimethyl-2-[(2-methylphenyl)amino]pyrimidin-4-one

5,6-Dimethyl-2-methylthiopyrimidin-4-one (Eur.J.Med. Chem. (1988), 23, 53) (24.0 g, 0.14 m) and o-toluidine (30 ml) were stirred together under nitrogen at 200-220°
20 for 12 hours with effluent gases being passed through a CHLOROS trap. After cooling the reaction mixture was triturated with pentane, the insoluble solid filtered off and crystallised from methanol/ethyl acetate to give the title compound (23.1 g), m.p. = 194-5°.

25

(ii) 4-Chloro-5,6-dimethyl-2-[(2-methylphenyl)amino]pyrimidine

The product of Example 18(i) above (13.0 g, 0.057 m)
30 and phosphorous oxychloride (200 ml) were heated together at reflux temperature for two hours. The POCl₃ was distilled off and ice added carefully to the residue which was then basified with sodium hydroxide. The aqueous

- 27 -

5 mixture was extracted with chloroform and the combined organic extracts dried and evaporated to dryness. The residue was chromatographed on silica gel in chloroform and appropriate fractions combined, evaporated and the residue triturated with pentane to yield the title compound as a solid (8.5 g), m.p. = 95-98°.

(iii) 5,6-Dimethyl-2-[(2-methylphenyl)amino]-4-(phenyl-amino)pyrimidine hydrochloride

10

The product of Example 18(ii) above (2.5 g, 0.01 m) and aniline (0.93 g, 0.01 m) were heated at reflux temperature in dry tetrahydrofuran (30 ml) for nine hours. The solid which crystallised out on cooling was filtered 15 off and re-crystallised from methanol/isopropanol/diethyl ether to yield the title compound (2.7 g) as its hydrochloride salt, m.p. = 257-259°.



Found: C 67.0, H 6.2, N 16.4, Cl⁻ 10.4
20 Requires: C 67.1, H 6.1, N 16.4, Cl⁻ 10.4

Example 19

25 5,6-Dimethyl-2-[(2-methylphenyl)amino]-4-(N-methyl-2-
methylphenyl amino)pyrimidine hydrochloride

A mixture of 4-chloro-5,6-dimethyl-2-[(2-methyl-phenyl)amino] pyrimidine (1.17 g, 0.005 m) and N-methyl-o-toluidine (6.0 ml) were heated together at 140° for six 30 hours. After cooling ether was added to remove excess N-methyl-o-toluidine. Decanting off the ether and crystallisation of the solid residue from isopropanol/ether gave the title compound (0.7 g) as its hydrochloride salt, m.p. = 192-194°.

- 28 -



Found: C 68.1, H 6.8, N 15.0

Requires: C 68.4, H 6.8, N 15.2

5

Example 20

10

5,6-Dimethyl-2-[(2-methylphenyl)amino]-4-(N-methyl-phenylamino)pyrimidine hydrochloride

A mixture of 4-chloro-5,6-dimethyl-2-[(2-methyl-phenyl)amino]pyrimidine (2.5 g, 0.01 m) and N-methylaniline (1.07 g, 0.01 m) in dry tetrahydrofuran (30 ml) was heated at reflux temperature for six hours. After cooling, ether was added to precipitate a solid which was collected, washed with ether and crystallised from isopropanol/ether to yield the title compound (1.61 g) as its hydrochloride salt, m.p. = 199-200°.

15



Found: C 67.8, H 6.6, N 15.3, Cl⁻ 9.8

20

Requires: C 67.8, H 6.5, N 15.8, Cl⁻ 10.0

Example 21

25

5-Methyl-6-n-propyl-2-[(2-methyl)phenylamino]-4-(N-methyl-2-methyl phenylamino)pyrimidine hydrochloride

(i) 2-[(2-Methylphenyl)amino]-5-methyl-6-n-propyl-pyrimidin-4-one

30

2-Methylthio-5-methyl-6-n-propylpyrimidin-4-one (C.A. 84, P164836n) (16.0 g, 0.08 m) and o-toluidine (30 ml) were heated together at 200° (oil-bath temp) for six hours.

- 29 -

After cooling, the mixture was triturated with pentane and the pentane decanted. The residual solid was crystallised from methanol/isopropylacetate to yield the title compound (10.5 g), m.p. = 192-194°.

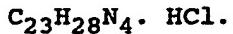
5

(ii) 4-Chloro-5-methyl-6-n-propyl-2-[(2-methylphenyl)-amino]pyrimidine

The product of Example 21(i) above and phosphorous oxychloride (50 ml) were heated together under reflux for two hours. The POCl_3 was distilled off and ice carefully added to the residue. The aqueous mixture was basified with sodium hydroxide and extracted with chloroform. The combined chloroform extracts were concentrated to a low volume and chromatographed on silica gel with chloroform as eluent. Appropriate fractions were combined and evaporated to an oil (11.0 g) which was used immediately below.

20 (iii) 5-Methyl-6-n-propyl-2-[(2-methylphenyl)amino]-4-(N-methyl-2-methylphenylamino)pyrimidine hydrochloride

The product of Example 21(ii) above (5.5 g, 0.02 m) and N-methyl-o-toluidine (2.4 g, 0.02 m) in tetrahydrofuran (45 ml) were heated together at reflux temperature for three hours, cooled and concentrated to a low volume. Ether was added and the precipitated solid collected, washed with ether and re-crystallised twice from isopropylacetate to give the title compound (1.05 g) as its hydrochloride salt, m.p. = 170-171°.



Found: C 69.6, H 7.4, N 13.9, Cl⁻ 8.8

Requires: C 69.6, H 7.4, N 14.1, Cl⁻ 8.9

- 30 -

Example 22

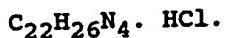
5-Methyl-6-n-propyl-2-[(2-methylphenyl)amino]-4-(N-methylphenylamino) pyrimidine hydrochloride

5

Substituting N-methylaniline (2.14 g, 0.02 mol) and using corresponding molar proportions of the other reagents in Example 21(iii) gave a crystalline solid directly from the tetrahydrofuran reaction mixture.

10

This was collected and washed with ether to give the title compound (4.5 g) as its hydrochloride salt, m.p. 178-179°.



Found: C 69.3, H 7.3, N 14.6, Cl⁻ 9.2

15

Requires: C 69.0, H 7.1, N 14.6, Cl⁻ 9.3

Example 23

2-[(2-Methylphenyl)amino]-4-(N-methylphenylamino)-
5,6,7,8-tetrahydroquinazoline hydrochloride !SK&F 99119!

(i) 2-Thioxo-5,6,7,8-tetrahydroquinazolin-4-one.

Sodium (8.5 g, 0.37 mol) was dissolved in absolute ethanol (300 mL) and treated with ethyl-2-oxocyclohexanecarboxylate (40 g, 0.186 mol) and thiourea (14.2 g, 0.186 mol) and refluxed for 4 hours. The solvent was removed in vacuo and the residual solid dissolved in water and made acidic with acetic acid. The solid was collected, washed with water and dried to give the title compound (32 g), m.p. = 305-308°.

- 31 -

(ii) 2-Methylthio-5,6,7,8-tetrahydroquinazolin-4-one.

2-Thioxo-5,6,7,8-tetrahydroquinazolin-4-one (18.2 g, 0.1 mol) was added to a solution of sodium hydroxide (4.4 g, 0.11 mol) in water (25 ml). Ethanol (100 ml) was introduced followed by methyl iodide (15.6 g, 0.11 mol) and the final solution stirred at 60° for two hours. The suspension was cooled and filtered and the solid washed with diethyl ether to give the title compound (17.6 g),
m.p. = 215-219°.

(iii) 2-[(2-Methylphenyl)amino]-5,6,7,8-tetrahydro-quinazolin-4-one

2-Methylthio-5,6,7,8-tetrahydroquinazolin-4-one (16.8 g, 0.085 mol) and o-toluidine (50 ml) were heated at 220° for 24 hours and allowed to cool. The effluent gases from this reaction were passed through a CHLOROS trap. The mixture was treated with 40-60 petroleum spirits and filtered and the solid collected and recrystallised from dimethyl sulphoxide/water to give the title compound (16.6 g), m.p. = 253-257°.

(iv) 4-Chloro-2-[(2-methylphenyl)amino]-5,6,7,8-tetrahydroquinazoline.

2-[(2-Methylphenyl)amino]-5,6,7,8-tetrahydro-quinazolin-4-one (16 g, 0.063 mol) and redistilled phosphorous oxychloride (50 ml) were heated to reflux temperature for three hours, allowed to cool and evaporated to dryness. The residual oil was treated with ice-water and extracted with chloroform. The combined organic extracts were washed with sodium

- 32 -

bicarbonate solution, water, dried and filtered. The residue after evaporation was chromatographed on silica gel using chloroform as eluent, the appropriate fractions combined and evaporated to give a solid which was 5 triturated with 60-80 petroleum spirits to give the title compound (6.1 g), m.p. = 116-124°.

(v) 2-[(2-Methylphenyl)amino]-4-(N-methylphenyl)amino-10 5,6,7,8-tetrahydroquinazoline hydrochloride.

10 4-Chloro-2-[(2-methylphenyl)amino]-5,6,7,8-tetrahydroquinazoline (2.73 g, 0.01 mol) and N-methyl aniline (1.07 g, 0.01 mol) were heated to reflux temperature in dioxane (50 ml) for sixteen hours and allowed to cool. 15 The solvent was removed in vacuo and the residue dissolved in petroleum spirits and filtered. The solid was recrystallised from ethanol/diethyl ether, filtered and the solid washed with ether to give the title compound (0.98 g), m.p. = 222-226°.

20 $C_{22}H_{24}N_4 \cdot HCl \cdot 0.7H_2O \cdot 0.1EtOH$

Found: C 66.70, H 6.50, N 13.86

Requires: C 67.14, H 6.59, N 14.10

Example 24

25 2-[(2-Methylphenyl)amino]-4-(N-methyl-2-methylphenylamino)-5,6,7,8-tetrahydroquinazoline hydrochloride. !SK&F 99118!

30 Substituting N-methyl-o-toluidine (1.21 g, 0.01 mol) for N-methyl aniline and using corresponding molar proportions of other reagents as in Example 23 above gave a mixture which was heated to reflux temperature for sixteen hours and allowed to cool. The solvent was removed in vacuo and the residual oil dissolved in

- 33 -

chloroform, washed twice with sodium bicarbonate solution, water, dried and filtered. The oil obtained from evaporation of the solvent was chromatographed on silica gel using chloroform as eluent, the appropriate fractions combined and evaporated to give a pale orange oil. This was dissolved in ethanolic HCl and the solvent removed to give an oil which was triturated with diethyl/ether to give a solid. This was recrystallised from ethanol/diethyl ether, filtered and washed with ether to give the title compound (0.42 g) m.p. = 227-228°.



Found: C 67.54, H 6.58, N 13.74, Cl⁻ 8.80

Requires: C 67.89, H 6.86, N 13.37, Cl⁻ 8.71

15

Example 25

2-[(2-Methylphenyl)amino]-4-(N-methylphenylamino)-cyclopenta[d]pyrimidine hydrochloride !SK&F 99149!

20 (i) 2-Methylthiocyclopenta[d]pyrimidin-4-one

Ethyl-2-oxocyclopentanecarboxylate (62.4 g, 0.4 mol) and S-methylthiouronium sulphate (111.2 g, 0.4 mol) were added to a solution of potassium hydroxide (36 g, 0.64 mol) 25 in methanol (500 ml) and stirred at room temperature for two hours. This was poured into water (3000 ml) and extracted with chloroform. The combined extracts were dried, filtered and the solvent evaporated to give a solid which was triturated with diethyl ether and filtered to 30 give the title compound (11.2 g) m.p. = 210-213°.

- 34 -

(ii) 2-[(2-Methylphenyl)amino]cyclopenta[d]pyrimidin-4-one.

2-Methylthiocyclopenta[d]pyrimidin-4-one (5.1 g, 0.028 mol) and o-toluidine 920 ml) were heated to 220° for
5 sixteen hours and allowed to cool to give an oil. The effluent gases from this reaction were passed through a CHLOROS trap. This was triturated with 40-60 petroleum spirits and a solid filtered off and washed with more solvent to give the title compound (6.8 g),
10 m.p. = 208-213°.

(iii) 4-Chloro-2-[(2-methylphenyl)amino]cyclopenta[d]-pyrimidine.

15 2-[(2-Methylphenyl)amino]cyclopenta[d]pyrimidin-4-one (6.7 g, 0.028 mol) and phosphorus oxychloride (70 ml) were heated together under reflux for three hours and then evaporated to dryness. The residual oil was added carefully to ice/ammonia solution and extracted with
20 chloroform. The combined extracts were washed with sodium bicarbonate solution, water, filtered and dried to give an oil. This was chromatographed on silica gel using chloroform as eluent and the appropriate fractions were combined, evaporated and the residue triturated with
25 40-60 petroleum spirits to give the title compound (2.1 g), m.p. 135-142°.

(iv) 2-[(2-Methylphenyl)amino])-4-(N-methylphenyl)amino-cyclopenta[d]pyrimidine hydrochloride.

30 4-Chloro-2-[(2-methylphenyl)amino]cyclopenta[d]-pyrimidine (1.0 g, 0.0038 mol) and N-methyl aniline (0.49 g, 0.0046 mol) were refluxed in dry dioxane (60 ml)

- 35 -

for sixteen hours. The mixture was evaporated to dryness and the resultant solid recrystallised from ethanol/diethyl ether, filtered and washed with ether to give the title compound (0.72 g), m.p = 210-218° (dec).

5 C₂₁H₂₂N₄ · HCl · H₂O

Found: C 65.28, H 6.25, N 14.33

Requires: C 65.53, H 6.55, N 14.55

Example 26

10

2-[(2-Methylphenyl)amino]-4-(N-methyl-2-methylphenyl-
amino)cyclopenta[d]pyrimidine hydrochloride. !SK&F 99148!

15 4-Chloro-2-[(2-methylphenyl)amino]cyclopenta[d]-pyrimidine (1.0 g, 0.0038 mol) and N-methyl-o-toluidine (0.59 g, 0.0046 mol) were refluxed in dry dioxane (60 ml) for sixteen hours. The mixture was evaporated to dryness and the resultant solid triturated with diethyl ether to give a solid which was recrystallised from ethanol/diethyl
20 ether, filtered and washed with diethyl ether to give the title compound (0.58 g), m.p. = 210-214°.

C₂₂H₂₄N₄ · HCl · 0.8H₂O

Found: C 66.55, H 6.42, N 14.22

Requires: C 66.83, H 6.78, N 14.17

Example 272-Amino-4-(2-methylphenylamino)-5-methyl-6-(methoxymethyl)pyrimidine

5

(i) Ethyl 2-methyl-3-oxo-4-methoxybutyrate

Zinc (36.12 g, 0.55 mol), methoxyacetonitrile (26.18 g, 0.37 mol), benzene (370 ml) and a small amount of mercuric chloride were heated to reflux under nitrogen. A solution of ethyl 2-bromopropionate (100 g, 0.55 mol) in benzene was added dropwise over 2.5 h, then reflux continued for a further hour before cooling to room temperature. 10% Aqueous sulphuric acid (650 ml) was added, and the layers separated. The aqueous was further extracted with ether (2 x 250 ml), and the combined organic layers washed with water and aqueous NaHCO_3 , then dried and evaporated. Distillation gave the title compound as an oil (36.53 g), b.p. 111°/12mm.

20

(ii) 2-Amino-5-methyl-6-methoxymethylpyrimidine-4-one

Guanidinium carbonate (8.8 g, 49 mmol) and ethyl 2-methyl-3-oxo-4-methoxybutyrate (17.0 g, 98 mmol) in ethanol (200 ml) were heated under reflux for 4.5 hours. The solvent was evaporated and the residue treated with ice-cold water (100 ml) and acidified to pH 5 with glacial acetic acid. The solid which precipitated was filtered off, washed with a small amount of cold water and dried to give the title compound (14.47 g), m.p. 237-239°C.

(iii) 2-Amino-4-chloro-5-methyl-6-methoxymethylpyrimidine

2-Amino-5-methyl-6-methoxymethylpyrimidine-4-one (7.0 g, 41 mmol) and phosphoryl chloride (21 ml) were heated at reflux for 70 min. Excess phosphoryl chloride

- 37 -

was evaporated off and the residue treated with ice (100 ml), then brought to pH 8 with ammonium hydroxide. The yellow solid was filtered off, and the filtrate reduced in volume to obtain further crops. The combined solids were
5 washed with cold water and dried to give the title compound (5.75 g), m.p. 201-203°C.

(iv) 2-Amino-4-(2-methylphenylamino)-5-methyl-6-methoxymethylpyrimidine

10 2-Amino-4-chloro-5-methyl-6-methoxymethylpyrimidine (5.65 g, 30 mmol) and o-toluidine (7.06 g, 66 mmol) in n-butanol (100 ml) were heated under reflux for 4.5 h. The solvent was evaporated, the residue triturated with ether,
15 and the solid filtered off and dissolved in a small volume of water. The solution was raised to pH 8 with ammonium hydroxide and extracted repeatedly with chloroform. The combined extracts were dried and evaporated, and the residue crystallised from chloroform/ether to give the
20 title compound (1.18 g), m.p. 148-149°C.



Found C 64.24, H 6.90, N 21.23

Requires C 63.97, H 7.09, N 21.31

25

Example 28

2-(2-Methylphenylamino)-4-(N-methylphenylamino)-6-aminopyrimidine hydrochloride

30 (i) 6-Amino-2-[(2-methylphenyl)amino]pyrimidin-4-one

6-Amino-2-(nitroamino)pyrimidin-4-one (4.28 g, 25 mmol) and o-toluidine (6.42 g, 60 mmol) were added to dry

- 38 -

pyridine (50 ml), and the mixture heated to reflux for 48 hours. The pyridine was evaporated in vacuo, and the oily residue boiled with ethyl acetate, then allowed to cool. The resulting solid was mainly unreacted starting material, and was filtered off and discarded (1.46 g).
5 The filtrate was extracted with aqueous sodium hydroxide, and the extracts neutralised with hydrochloric acid and re-extracted with ethyl acetate. Drying and evaporation of the organic extracts, and trituration with ether gave
10 the title compound (2.3 g, 42%), m.p. 142-147°C.

(ii) 4-Amino-6-chloro-2[(2-methylphenyl)amino]pyrimidine

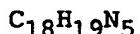
6-Amino-2-[(2-methylphenyl)amino]pyrimidin-4-one

15 (2.0 g, 9.26 mmol) and phosphoryl chloride (20 ml, excess) were heated to reflux for 1 hour, then the solution was cooled and poured onto ice. The dark oil was extracted into ethyl acetate, then the aqueous layer was neutralised with sodium hydroxide and re-extracted with ethyl acetate.
20 The combined organic extracts were washed with aqueous sodium carbonate, water and brine, dried and evaporated to a brown tar (1.2 g), which was used immediately without further purification.
25 (iii) 2-(2-Methylphenylamino)-4-(N-methylphenylamino)-6-aminopyrimidine hydrochloride

A mixture of 6-amino-4-chloro-2-[(2-methylphenyl)amino]pyrimidine (1.2 g, 5.1 mmol) and N-methylaniline (3.0 g, excess) was heated to 170°C for 4 hours, then allowed to cool. The tarry product was washed with 1:1 ether/pet. ether, then chromatographed (silica, 0-1st MeOH in CH₂Cl₂). Product fractions were evaporated and

- 39 -

converted to the hydrochloride, which crystallised from ethanol/ether (0.08g), m.p. 218-220°C. A second crop (0.18 g) was obtained from the mother liquors.



5 Found C 63.00, H 5.99, N 20.20
Requires C 63.24, H 5.90, N 20.49

Example 29

10 2-(2-Methylphenylamino)-4-(N-methylphenylamino)-5-propyl-6-methylpyrimidine hydrochloride

(i) Ethyl 2-propyl-3-oxobutyrate

15 To a solution of ethyl acetoacetate (39.04 g, 0.3 mol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (45.67 g, 0.3 mol) in dry benzene (500 ml) was added a solution of 1-iodopropane (51.0 g, 0.3 mol) in dry benzene (200 ml). The mixture was stirred for 3h, then the solid which
20 precipitated was filtered off, washed with water, dried and evaporated in vacuo. The resulting brown oil was distilled twice under reduced pressure to give the title compound as a clear oil, yield 18.06 g, b.p. 80°C/18 mm.

25 (ii) 6-Methyl-2-thioxo-2-oxo-5-propylpyrimidine

Sodium (4.14 g, 0.18 mol) was dissolved in ethanol (150 ml), and a solution of ethyl 2-propyl-3-oxobutyrate (15.46 g, 0.09 mol) in ethanol was added, followed by
30 thiourea (6.48 g, 0.09 mol). The mixture was heated under reflux for 4h, then the solvent was evaporated. The residue was dissolved in water and acidified to pH 4

- 40 -

with glacial acetic acid. The white solid which precipitated was filtered off, washed with water and dried to give the title compound (8.97 g), m.p. 207-208°C.

5 (iii) 2-Methylthio-5-propyl-6-methylpyrimidin-4-one

To a solution of sodium hydroxide (2.2 g, 55 mmol) in water (75 ml) was added 6-methyl-2-thioxo-4-oxo-5-propylpyrimidine (9.46 g, 50 mmol), followed by 10 iodomethane (7.81 g, 55 mmol). The mixture was heated under reflux for 3h, then stirred at room temp. for 16h. Excess iodomethane was evaporated off, and the solution acidified to pH 4 with glacial acetic acid. The white solid which precipitated was filtered off, washed with 15 water and dried to give the title compound (9.88 g), m.p. 178°C.

(iv) 2-(2-Methylphenylamino)-5-propyl-6-methylpyrimidin-4-one

20 2-Methylthio-5-propyl-6-methylpyrimidin-4-one (9.76 g, 49.2 mmol) and 2-methylaniline (37 ml, 350 mmol) were heated with stirring at 170°C for 17h. Excess toluidine was distilled off in vacuo, and the residue boiled with 25 ethanol to give a white solid, which was filtered off, washed and dried to give the title compound (9.35 g), m.p. 223°C.

(v) 2-(2-Methylphenylamino)-4-chloro-5-propyl-6-methylpyrimidine

2-(2-Methylphenylamino)-5-propyl-6-methylpyrimidin-4-one (4.0 g, 15.5 mmol) and phosphoryl chloride (12 ml, excess) were heated under reflux for 3h. Excess 35 phosphoryl chloride was evaporated off, and the residue

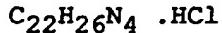
- 41 -

treated with ice-water. The mixture was extracted with chloroform, washed with aqueous sodium bicarbonate, dried and evaporated to give the product as a yellow oil which crystallised on standing; yield 3.68 g, m.p. 94-96°C.

5

(vi) 2-(2-Methylphenylamino)-4-(N-methylphenylamino)-5-propyl-6-methylpyrimidine hydrochloride

A solution of 2-(2-methylphenylamino)-4-chloro-5-propyl-6-methylpyrimidine (1.8 g, 6.53 mmol) and N-methylaniline (0.84 g, 7.84 mmol) in dioxan (20 ml) was heated under reflux for 17h. The solvent was evaporated, then the residue was boiled with ethanol and filtered hot. On allowing to cool, the filtrate deposited a yellow solid, which was filtered off and recrystallised from ethanol; yield 0.73 g, m.p. 258°C.



Found C 68.88, H 7.22, N 14.60
Requires C 69.00, H 7.11, N 14.63

20

Example 30

2-(2-Methylphenylamino)-4-(N-methylphenylamino)-5-(2-benzyl oxyethyl)-6-methylpyrimidine

25

(i) 6-Methyl-2-thioxo-4-oxo-5-(2-hydroxyethyl)pyrimidine

2-Acetylbutyrolactone (64 g, 0.5 mol) and thiourea (38 g, 0.5 mol) were added to a solution of sodium (23 g, 30 1.0 mol) in absolute ethanol (600 ml). The mixture was stirred under reflux for 4 hours, then allowed to stand overnight. The solvent was removed by evaporation, the

- 42 -

residual solid was dissolved in water (500 ml), and the solution acidified with acetic acid. The deposited solid was filtered off, washed with water and dried; yield 34.8 g (40%), m.p. 264-272°C.

5

(ii) 6-Methyl-2-methylthio-4-oxo-5-(2-hydroxyethyl)-pyrimidine

A suspension of 6-methyl-2-thioxo-4-oxo-5-(2-hydroxyethyl)pyrimidine (10.0 g, 0.053 mol) in absolute ethanol (100 ml) was added to a solution of sodium hydroxide (2.4 g, 0.104 mol) in water (50 ml). Methyl iodide (8.4 g, 0.059 mol) was added and the mixture was stirred under reflux for 4 hours, then allowed to cool. The deposited solid was filtered off, washed with water and dried; yield 6.0 g (60%), m.p. 186-190°C.

(iii) 6-Methyl-2-methylthio-4-oxo-5-(2-benzyloxyethyl)pyrimidine

20

6-Methyl-2-methylthio-4-oxo-5-(2-hydroxyethyl)-pyrimidine (32.2 g, 0.186 mol) was added in portions to a stirred suspension of pet. ether-washed 60% sodium hydride (17.5 g, 0.437 mol) in dry dimethylformamide (400 ml) at a temperature of 30-40°C. The mixture was stirred for 30 min at this temperature, then a solution of benzyl bromide (32.9 g, 0.192 mol) in dimethylformamide (50 ml) was added dropwise over 10 min to the stirred mixture. The mixture was stirred for 1 hour at room temperature, then poured into a solution of water (500 ml) containing ammonium chloride, and allowed to stand. The deposited solid was filtered off, dried, and recrystallized from ethyl acetate. The product was collected as a white solid; yield 29.5 g (57%), m.p.-139-144°C.

35

- 43 -

(iv) 6-Methyl-2-[(2-methylphenyl)amino]-4-oxo-5-(2-benzyloxyethyl)pyrimidine

A mixture of 6-methyl-2-methylthio-4-oxo-5-(2-benzyloxyethyl)pyrimidine (29 g, 0.104 mol) and o-toluidine (150 ml, excess) was stirred at 200°C for 16 hours, then allowed to stand overnight. The solidified residue was triturated with diethyl ether to obtain the title compound; yield 29.9 g (82%), m.p. 162-168°C.

10

(v) 6-Methyl-2-[(2-methylphenyl)amino]-4-chloro-5-(2-benzyloxyethyl)pyrimidine

A mixture of 6-methyl-2-[(2-methylphenyl)amino]-4-oxo-5-(2-benzyloxyethyl)pyrimidine (25 g, 0.071 mol) and phosphoryl chloride (150 ml, excess) was stirred under reflux for 1 hour, the excess phosphoryl chloride removed by evaporation, and the residual oil treated with an excess of ice/water. The crude product was extracted with chloroform, the organic layer washed with saturated sodium bicarbonate and water, dried over MgSO₄ and the solvent evaporated, the product being a pale yellow viscous oil; yield 14 g.

25 (vi) 6-Methyl-2-[(2-Methylphenyl)amino]-4-(N-methylphenylamino)-5-(2-benzyloxyethyl)pyrimidine

A mixture of 6-methyl-2-[(2-methylphenylamino)-4-chloro-5-(2-benzyloxyethyl)pyrimidine (1.0 g, 2.72 mmol) and an excess of N-methylaniline (3 ml) was stirred and heated at 180-200°C for 2 hours. After cooling, the crude oil was purified by chromatography (silica gel, chloroform). A further 2 columns were required to obtain the product as a viscous oil; yield 200 mg.

- 44 -



Calc: C 72.95, H 6.60, N 12.06

Found: C 73.05, H 6.62, N 12.03

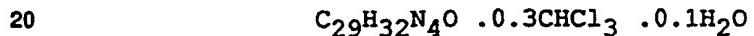
5

Example 31

2-(2-Methylphenylamino)-4-(N-methyl-2-methylphenylamino)-5-(2-benzyloxyethyl)-6-methylpyrimidine

- 10 (i) 6-Methyl-2-[(2-methylphenyl)amino]-4-[N-methyl-(2-methylphenyl)amino]-5-(2-benzyloxyethyl)pyrimidine

A mixture of 6-methyl-2-[(2-methylphenyl)amino]-4-chloro-5-(2-benzyloxyethyl)pyrimidine (2.0 g, 0.0544 mol) 15 and N-methyl-o-tolidine (5 ml, excess) was stirred at 200°C for 2 hours. After cooling, the crude residue was purified by silica gel chromatography, eluted with CHCl₃. A second column was required to obtain the product as a pale orange-coloured oil; yield 0.2 g.



Calc: C 71.79, H 6.68, N 11.43

Found: C 71.75, H 6.70, N 11.53

Example 32

25

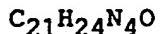
2-(2-Methylphenylamino)-4-(N-methylphenylamino)-5-(2-hydroxyethyl)-6-methylpyrimidine

- 30 6-Methyl-2-[(2-methylphenyl)amino]-4-(N-methylphenylamino)-5-(2-benzyloxyethyl)pyrimidine (2.3 g, 5.25 mmol) was mixed with 10% palladium on carbon in absolute ethanol (100 ml) and hydrogenated at 50 psi and

- 45 -

50°C for 12 hours. The product obtained by evaporation of the filtrate was crystallized from ethanol/diethyl ether and finally purified by silica gel chromatography, eluted with CHCl₃/MeOH (25:1). The product was obtained as a

5 pale grey solid; yield 0.4 g (22%), m.p. 98-100°C.



Calc: C 72.39, H 6.94, N 16.08

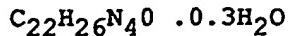
Found: C 72.11, H 7.04, N 15.90

10

Example 33

2-(2-Methylphenylamino)-4-(N-methyl-2-methylphenylamino)(-
5-(2-hydroxyethyl)-6-methylpyrimidine

15 A mixture of 6-methyl-2-[(2-methylphenylamino)-4-(N-methyl-2-methylphenylamino)-5-(2-benzyloxyethyl)pyrimidine (0.7 g, 1.55 mmol) and 10% palladium on carbon catalyst (0.35 g) in absolute ethanol (50 ml) was hydrogenated at 50 psi and 50°C for 6 hours, followed by further reduction
20 for 4 hours with fresh catalyst. After separation of the catalyst the filtrate was chromatographed (silica gel, CHCl₃/MeOH (25:1)). Product fractions were evaporated and triturated with pet. ether to give the title compound as a white crystalline solid; yield 0.13 g (23%), m.p. 161-
25 163°C.



Calc: C 71.82, H 7.28, N 15.32

Found: C 71.57, H 7.11, N 14.93

- 46 -

Example 34

2-(2-Methylphenylamino)-4-(N-methylphenylamino)-6-(benzyloxymethyl)pyrimidine hydrochloride

5

(i) 2-Thioxo-6-(benzyloxymethyl)pyrimid-4-one

To a solution of sodium (5.26 g, 0.224 mol) in ethanol (250 ml) was added thiourea (8.69 g, 0.114 mol) and ethyl 10 4-benzyloxycetoacetate (27.0 g, 0.114 mol) and the mixture heated under reflux for 3 hours. The solvent was evaporated off and water (300 ml) added, followed by glacial acetic acid to pH 4. The resulting solid was filtered, washed and dried to give the title compound 15 (22.12 g), m.p. 182-185°C.

(ii) 2-Methylthio-6-(benzyloxymethyl)pyrimid-4-one

To a solution of sodium hydroxide (2.3 g, 0.0581 mol) 20 in water (15 ml) was added 2-thioxo-6-(benzyloxymethyl)-pyrimid-4-one in ethanol (150 ml) and iodomethane (8.25 g, 0.0581 mol). The mixture was stirred at room temperature for 16 hours. The resulting solid was filtered off, washed and dried to yield the title compound (9.20 g), 25 m.p. 156-158°C.

(iii) 2-(2-Methylphenylamino)-6-(benzyloxymethyl)-pyrimid-4-one

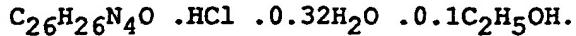
30 2-Methylthio-6-(benzyloxymethyl)pyrimid-4-one (13.0 g, 0.065 mol) and o-toluidine (20.856 g, 0.195 mol) were heated with stirring under nitrogen at 200°C for 16 hours. After cooling, the mixture was triturated with ether 35 to give a brown solid which was filtered off, washed and dried (11.30 g) m.p. 95-98°C.

- 47 -

(iv) 2-(2-Methylphenylamino)-4-chloro-6-(benzyloxy-methyl)pyrimidine.

- 2- (2-Methylphenylamino)-6- (benzyloxy-methyl)pyrimid-4-one (3.14 g, 0.0098 mol) and phosphoryl chloride (30 ml, excess) were heated with stirring under reflux for 1 hour. The phosphoryl chloride was evaporated off and the residue poured onto iced water, neutralised and extracted with chloroform. The combined extracts were dried, filtered and evaporated to an oil. This was purified by flash chromatography (silica, dichloromethane / 40-60 petroleum ether) to give the title compound as a yellow oil (1.33 g).
- 15 (v) 2-(2-Methylphenylamino)-4-(N-methylphenylamino)-6-(benzyloxymethyl)pyrimidine hydrochloride.

2- (2-Methylphenylamino)-4-chloro-6-(benzyloxymethyl)pyrimidine (1.33 g, 0.0039 mol) and N-methylaniline (0.5 g, 0.0047 mol) in 1,4-dioxane were stirred and heated under reflux for 16 hours. The solvent was evaporated off and the residue triturated with ether to give a white solid. This was filtered off, recrystallised from methanol/ether and dried to give the title compound (0.6 g), m.p. 180°C.



Found: C 69.04, H 6.09, N 12.28

Requires: C 68.80, H 6.22, N 12.26

30

Example 35

2-(2-Methylphenylamino)-4-(N-methylphenylamino)-6-methoxymethylpyrimidine hydrochloride

35 (i) 2-Methylthio-6-(methoxymethyl)pyrimid-4-one

- 48 -

To a solution of potassium hydroxide (92.1 g, 1.642 mol) in methanol (2500 ml) was added methyl 4-methoxyacetoacetate (150 g, 1.026 mol) and 2-methyl-2-thiopseudourea sulphate (285.6 g, 1.026 mol). The mixture 5 was stirred at room temperature for 3 hours. The solvent was evaporated off and water (500 ml) added, followed by glacial acetic acid to pH 4. The resulting solid was filtered off, washed and dried to yield the title compound (166.02 g), m.p. 184-186°C.

10

(ii) 2-(2-Methylphenylamino)-6-(methoxymethyl)pyrimid-4-one

2-Methylthio-6-methoxymethylpyrimid-4-one (80 g, 0.43 mol) and o-toluidine (138.55 g, 1.29 mol) were heated to 15 200°C under nitrogen with stirring for 16 hours. On cooling the product crystallised out and was filtered off, washed with ether and dried to yield the title compound (86.12 g), m.p. 140-145°C.

20 (iii) 2-(2-Methylphenylamino)-4-chloro-6-(methoxymethyl)pyrimidine.

2-(2-Methylphenylamino)-6-methoxymethylpyrimid-4-one (86.0 g, 0.351 mol) and phosphoryl chloride (500 ml, excess) were heated with stirring under reflux for 1 hour. The excess phosphoryl chloride was evaporated off and the residue poured onto iced water, neutralised and extracted using chloroform (x3). The combined extracts were dried, filtered and evaporated to an oil. This was purified by 30 flash chromatography (silica, dichloromethane / 40-60 petroleum ether) to give the title compound as a yellow oil (66.0 g).

- 49 -

(iv) 2-(2-Methylphenylamino)-4-(N-methylphenylamino)-6-(methoxymethyl)pyrimidine hydrochloride.

2-(2-Methylphenylamino)-4-chloro-6-

- 5 (methoxymethyl)pyrimidine (37.0 g, 0.141 mol) and N-methylaniline (18.10 g, 0.169 mol) in 1,4-dioxane were stirred and heated under reflux for 16 hours. On cooling, the product crystallised out and was filtered off, washed and recrystallised from ethanol to give the title compound
10 (19.36 g), m.p. 205-207°C.



Found: C 64.27, H 6.39, N 14.58

Requires: C 64.77, H 6.25, N 15.11

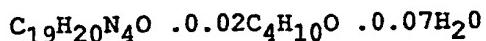
15

Example 36

2-(2-Methylphenylamino)-4-(N-methylphenylamino)-6-hydroxymethylpyrimidine

- 20 To a solution of 2-(2-methylphenylamino)-4-(N-methylphenylamino)-6-(methoxymethyl)pyrimidine hydrochloride (5.0 g, 0.0135 mol) in dichloromethane (25 ml) was added dropwise boron tribromide (16.93 g, 0.0676 mol) in dichloromethane (5 ml), keeping the
25 temperature between -10 & 0°C. After a further hour at 0°C, the solution was poured on to iced water and basified to pH 14 using sodium hydroxide. The mixture was extracted using dichloromethane (x3), and the combined extracts dried, filtered and evaporated. The residue was
30 purified using flash chromatography (silica, methanol/dichloromethane), triturated with ether and the resulting crystals filtered and dried to yield the title compound (3.94 g), m.p. 134-136°C.

- 50 -



Found: C 70.75, H 6.34, N 17.14

Requires: C 71.23, H 6.29, N 17.49

5

Example 37

2-(2-Methylphenylamino)-4-(N-methylphenylamino)pyrimidine-
6-carboxaldehyde

10

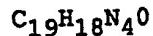
To a stirring solution of oxalyl chloride (2.094 g, 0.0165 mol) in dichloromethane (50 ml) at -50°C was added dimethylsulphoxide (2.808 g, 0.036 mol) in dichloromethane (10 ml) dropwise, keeping the temperature below -50°C.

15

After 10 mins, a solution of 2-(2-methylphenylamino)-4-(N-methylphenylamino)-6-(hydroxymethyl)pyrimidine (5 g, 0.015 mol) in dichloromethane (50 ml) was added dropwise over 15 mins and stirred for a further 30 mins.

20

Triethylamine (3.821 g, 0.375 mol) was then added and the mixture allowed to warm to room temperature. Water (100 ml) was added and the mixture extracted with dichloromethane (x2). The organic extracts were combined, dried, filtered and evaporated. The residue was purified by flash chromatography (silica, dichloromethane/methanol) then recrystallised from acetone-water to yield the title compound (2.1 g), m.p. 115-117°C.



Found: C 71.57, H 5.58, N 17.65

Requires: C 71.68, H 5.70, N 17.60

30

- 51 -

Example 38

2-(2-Methylphenylamino)-4-(N-methylphenylamino)-6-(methylthiomethyl)pyrimidine

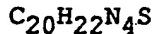
5

(i) 2-(2-Methylphenylamino)-4-(N-methylphenylamino)-6-(bromomethyl)pyrimidine

To a stirred solution of 2-(2-methylphenylamino)-4-(N-methylphenylamino)-6-(hydroxymethyl)pyrimidine (5 g, 0.015 mol) in ether (100 ml) was added carbon tetrabromide (9.95 g, 0.03 mol) and triphenylphosphine (7.87 g, 0.03 mol). After 48 hours the ether was evaporated off and the residue purified by flash chromatography (silica, dichloromethane) to give an oil. This was triturated with 40-60 petroleum ether and the resulting solid filtered off, washed and dried (4.20 g).

(ii) 2-(2-Methylphenylamino)-4-(N-methylphenylamino)-6-(methylthiomethyl)pyrimidine

Sodium thiomethoxide (1.097 g, 0.0157 mol) and 2-(2-methylphenylamino)-4-(N-methylphenylamino)-6-(bromomethyl)pyrimidine (3.0 g, 0.0078 mol) in methanol (150 ml) were stirred at room temperature for 16 hours. The solvent was evaporated off and the residue treated with water, then extracted with dichloromethane (x2). The organic extracts were combined, dried, filtered and evaporated, and the residue crystallised from acetonitrile to yield the title compound (2.23 g), m.p. 137-140°C.



Found: C 68.69, H 6.32, N 16.08

Requires: C 68.54, H 6.33, N 15.99

- 52 -

Example 39

2-(2-Methylphenylamino)-4-(N-methylphenylamino)-5-methyl-6-(methoxymethyl)pyrimidine hydrochloride

5

(i) Ethyl-2-methyl-4-methoxyacetoacetate

To a stirring mixture of zinc (90.25 g, 1.38 mol) and mercuric chloride (trace) in dry benzene (1000 ml) under 10 nitrogen was added methoxyacetonitrile (65.32 g, 0.92 mol). The reaction was heated to reflux for 15 minutes, then ethyl bromopropionate in dry benzene (500 ml) added dropwise over 2.5 hours and refluxed for a further hour. After cooling, 10% sulphuric acid (1800 ml) was added and 15 the mixture extracted with ether (x3). The extracts were washed with dilute sodium bicarbonate, dried, filtered and evaporated to an oil. Distillation under reduced pressure gave the title compound (91.2 g), b.p. 100-116°C/9mm.

20

(ii) 2-Methylthio-5-methyl-6-(methoxymethyl)pyrimid-4-one

To a solution of potassium hydroxide (44.88 g, 0.8 mol) in methanol (1.2 l) was added ethyl-2-methyl-4-methoxyacetoacetate (87.1 g, 0.5 mol) and 2-methyl-2-thiopseudourea sulphate (139.2 g, 0.5 mol). The mixture was stirred at room temperature for 3 hours, the solvent evaporated off, and water (350 ml) added, followed by glacial acetic acid to pH 4. The resulting solid was 30 filtered off, washed and dried to yield the title compound (78.00 g), m.p. 184-186°C.

(iii) 2-(2-Methylphenylamino)-5-methyl-6-(methoxymethyl)pyrimid-4-one

35

- 53 -

2-methylthio-5-methyl-6-(methoxymethyl)pyrimid-4-one (78 g, 0.39 mol) and o-toluidine (167.00 g, 1.56 mol) were heated to 200°C under nitrogen with stirring for 16 hours. On trituration with ether the product crystallised out and 5 was filtered off, washed and dried (88 g), m.p. 174-176°C.

(iv) 2-(2-Methylphenylamino)-4-chloro-5-methyl-6-(methoxymethyl)pyrimidine.

- 10 2-(2-Methylphenylamino)-5-methyl-6-(methoxymethyl)-pyrimid-4-one (68.0 g, 0.26 mol) and phosphoryl chloride (500 ml, excess) were heated with stirring under reflux for 1 hour. The excess phosphoryl chloride was evaporated off and the residue poured onto iced water, 15 neutralised with sodium bicarbonate and extracted using chloroform (x3). The combined extracts were dried, filtered and evaporated to yield the title compound as an oil (70.82 g).
- 20 (v) 2-(2-Methylphenylamino)-4-(N-methylphenylamino)-5-methyl-6-(methoxymethyl)pyrimidine hydrochloride.

2-(2-Methylphenylamino)-4-chloro-5-methyl-6-(methoxymethyl)pyrimidine (9.0 g, 0.032 mol) and N-methylaniline (4.109 g, 0.038 mol) in 1,4-dioxane (350 ml) were stirred and heated under reflux for 16 hours. On cooling the product crystallised out, and was filtered off, washed and recrystallised from acetone-ether to give the title compound (12.32 g), m.p. 167-168°C.

30 $C_{21}H_{24}N_4O \cdot HCl$

Found: C 65.73, H 6.57, N 14.43

Requires: C 65.53, H 6.55, N 14.56

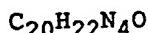
- 54 -

Example 40

2-(2-Methylphenylamino)-4-(N-methylphenylamino)-5-methyl-6-(hydroxymethyl)pyrimidine

5

2-(2-Methylphenylamino)-4-(N-methylphenylamino)-5-methyl-6-(methoxymethyl)pyrimidine hydrochloride (5.6 g, 0.0137 mol) in dichloromethane (25 ml) was cooled to -10°C and boron tribromide (17.18 g, 0.685 mol) in dichloromethane (10 ml) added dropwise, keeping the temperature between -10 & 0°C. After a further 30 minutes at 0°C the solution was poured on to iced water, basified to pH 14 using sodium hydroxide and extracted using dichloromethane (x3). The organic extracts were combined, dried, filtered and evaporated. The residue was recrystallised from ethanol and the resulting crystals filtered off, washed and dried to yield the title compound (4.58 g), m.p. 129-130°C.



20 Found: C 71.54, H 6.67, N 16.48
Requires: C 71.83, H 6.63, N 17.75

Example 41

25 2-(2-Phenylamino)-4-(N-methylphenylamino)-5,6,7,8-tetrahydroquinazoline hydrochloride

(i) 2-Methylthio-4-oxo-5,6,7,8-tetrahydroquinazoline

30 Ethyl 2-oxocyclohexanecarboxylate (53 g, 0.312 mol) and S-methyl thiouronium sulphate (82 g, 0.312 mol) were added to a solution of potassium hydroxide (28 g, 0.5 mol) in methanol (500 ml). The mixture was stirred at room

- 55 -

temperature for 16h, poured into water (1.5 l), acidified with glacial acetic acid, and stirred for 30 min before filtering off the product, washing with water and drying; yield 36 g (55%), m.p. 233-240°C.

5

(ii) 2-(Phenylamino)-4-oxo-5,6,7,8-tetrahydroquinazoline

- A mixture of 2-methylthio-4-oxo-5,6,7,8-tetrahydroquinazoline (20 g, 0.102 mol) and aniline (50 ml, excess) was heated at 200°C for 16h, then allowed to cool. The solid mass was triturated with ether, and the solid product filtered off, washed with ether and dried; yield 21 g (85%), m.p. 267-270°C.
- 15 (iii) 4-Chloro-2-(2-phenylamino)-5,6,7,8-tetrahydroquinazoline

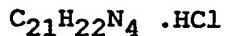
2-Phenylamino-4-oxo-5,6,7,8-tetrahydroquinazoline (10 g, 41.4 mmol) and phosphoryl chloride (100 ml, excess) were heated under reflux for 3 hours, then evaporated to dryness. The oil was added carefully to ice/ammonia, and extracted with chloroform. The extracts were washed with sodium bicarbonate solution and water, dried and evaporated to give an oil, which was triturated with ether to obtain the title compound; yield 7.1 g (67%), m.p. 123-125°C.

30

(iv) 2-(2-Phenylamino)-4-(N-methylphenylamino)-5,6,7,8-tetrahydroquinazoline hydrochloride

4-Chloro-2-(2-phenylamino)-5,6,7,8-tetrahydroquinazoline (2.0 g, 77 mmol) and N-methylaniline (5 ml, excess) were heated to 200°C for 3 hours. Chromatography (silica, chloroform), conversion to the hydrochloride and crystallisation from ethanol/ether gave the title compound (0.48 g, 19%), m.p. 242-245°C.

- 56 -



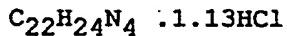
Found C 68.49, H 6.44, N 15.22, Cl 9.63
Requires C 68.74, H 6.32, N 15.27, Cl 9.66

5

Example 42

2-(2-Phenylamino)-4-(N-methyl-2-methylphenylamino)-5,6,7,8-tetrahydroquinazoline hydrochloride

- 10 A mixture of 4-chloro-2-(phenylamino)-5,6,7,8-tetrahydroquinazoline (4.0 g, 15.4 mmol) and N-methyl-2-methylaniline (10 ml, excess) was heated to 200°C for 2 hours. Chromatography (silica, chloroform), conversion to the hydrochloride and crystallisation from
15 ethanol/ether gave the title compound (0.28 g), m.p. 240-255°C.



Found C 68.36, H 6.57, N 14.32, Cl 10.08
Requires C 68.51, H 6.51, N 14.53, Cl 10.39

20

Example 43

2-(2-Methylphenylamino)-4-(N-methylphenylamino)-thiopyrano[3,2-d]pyrimidine hydrochloride

- 25 (i) 7,8-Dihydro-4-hydroxy-2-(2-methylphenylamino)-6H-thiopyrano[3,2-d]pyrimidine

- 30 7,8-Dihydro-4-hydroxy-2-methylthio-6H-thiopyrano[3,2-d]pyrimidine (5 g, 0.023 mol) and 2-methylphenylamine (10 g) were heated at 200°C for 20h. After allowing to cool, the reaction mixture was diluted with methanol, and

- 57 -

the resulting solid was collected by filtration, washed with methanol and dried; yield 4.8 g, m.p. 220-224°C.

(ii) 7,8-Dihydro-4-chloro-2-(2-methylphenylamino)-6H-
5 thiopyrano[3,2-d]pyrimidine

7,8-Dihydro-4-hydroxy-2-methylthio-6H-thiopyrano[3,2-d]pyrimidine (4 g, 0.014 mol) and phosphorus oxychloride (40 ml) were heated under reflux for 1h. The excess 10 phosphorus oxychloride was evaporated under reduced pressure. The residue was treated with ice/water, basified with conc. ammonia solution and extracted with chloroform (3x150 ml). The chloroform extracts were combined, dried over magnesium sulphate, filtered and evaporated under 15 reduced pressure to give the title compound as an oil; yield 4.2 g.

(iii) 7,8-Dihydro-4-(N-methylphenylamino)-2-(2-methylphenylamino)-6H-thiopyrano[3,2-d]pyrimidine
20 hydrochloride.

7,8-Dihydro-4-chloro-2-(2-methylphenylamino)-6H-thiopyrano[3,2-d]pyrimidine (3 g, 0.01 mol) and N-methylaniline (2.2 g, 0.02 mol) were heated at 150°C for 25 1h. After allowing to cool down the reaction mixture was diluted with diethyl ether, and the resulting solid was collected by filtration, washed with ether and dried. The solid was recrystallized from ethanolic HCl, then ethanol, to give the title compound; yield 1.4 g, m.p. 224-226°C.

30 $C_{21}H_{22}N_4S \cdot HCl$

Found C 62.93, H 5.79, N 13.74, S 7.81, Cl 8.81

Requires C 63.22, H 5.81, N 14.04, S 8.04, Cl 8.89

- 58 -

Example 44

2-(2-Methylphenylamino)-4-(N-methylphenylamino)-5,7-
dihydrothieno[3,4-d]pyrimidine hydrochloride

5

- (i) 2-(2-Methylthio)-4-oxo-5,7-dihydrothieno[3,4-d]pyrimidine

Methyl-3-oxotetrahydrothiophene-4-carboxylate (32.0 g,
10 0.2 mol) and S-methylisothiouranium sulphate (55.6 g, 0.2
mol) were added to a solution of potassium hydroxide
(17.9 g, 0.32 mol) in methanol (300 ml). The mixture was
stirred at room temperature for 16 hours, then poured into
water (approx. 3 l). The mixture was acidified with
15 acetic acid, the white solid filtered off, washed with
water and dried; yield 34.2 g (85%), m.p. 270-273°C.

- (ii) 2-[(2-Methylphenyl)amino]-4-oxo-5,7-dihydrothieno[3,4-d]pyrimidine

20

2-(2-Methylthio)-4-oxo-5,7-dihydrothieno[3,4-d]pyrimidine (32 g, 0.16 mol) was mixed with o-toluidine
(100 ml, excess) and the mixture stirred and heated at
200°C for 6 hours, then allowed to cool. The solid mass
25 was triturated with diethyl ether, and the grey
coloured solid filtered off, washed with ether and dried;
yield 30 g (73%), m.p. 247-251°C.

- (iii) 2-[(2-Methylphenyl)amino]-4-chloro-5,7-dihydrothieno[3,4-d]pyrimidine

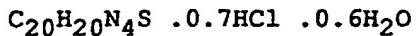
2-[(2-Methylphenyl)amino]-4-oxo-5,7-dihydrothieno[3,4-d]pyrimidine (30 g, 0.115 mol) was mixed with
phosphoryl chloride (150 ml, excess) and the mixture was

- 59 -

stirred under reflux for 2 hours, then evaporated to dryness. The residual oil was treated with ice-water, extracted with 3 x 100 ml CHCl₃, the extracts washed with sat. NaHCO₃ and water, dried over MgSO₄, and the solvent 5 evaporated. The dark oil was purified by silica gel chromatography and eluted with CHCl₃; yield 6.0 g (18%).

(iv) 2-[(2-Methylphenyl)amino]-4-(N-methyl-2-méthylphenyl)amino-5,7-dihydrothieno[3,4-d]pyrimidine

10 2-[(2-Methylphenyl)amino]-4-chloro-5,7-dihydrothieno[3,4-d]pyrimidine (2.0 g, 7.22 mmol) was mixed with N-methyl aniline (0.91 g, 8.59 mmol) in 1,4-dioxane (80 ml). The mixture was stirred under reflux for 15 16 hours, then evaporated to dryness. The residual solid was triturated with diethyl ether then recrystallized from aqueous ethanol; yield 1.4 g (58%), m.p. 195-198°C.



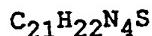
Calc: C 62.43, H 5.73, N 14.56, Cl 6.45
20 Found: C 62.57, H 5.53, N 14.71, Cl 6.64

Example 45

2-(2-Methylphenylamino)-4-(N-methyl-2-methylphenylamino)-25 5,7-dihydrothieno[3,4-d]pyrimidine

2-[2-(2-methylphenyl)amino]-4-chloro-5,7-dihydrothieno[3,4-d]pyrimidine (5.0 g, 0.018 mol) was mixed with N-methyl-o-toluidine (2.79 g, 0.0216 mol) and 30 fused at 160°C for 2 hours. After cooling, the oil was triturated with diethyl ether and the resulting solid filtered off and chromatographed (silica gel, CHCl₃); yield 2.76 g (42%), m.p. 162-165°C.

- 60 -



Calc: C 69.58, H 6.11, N 15.46, S 8.85

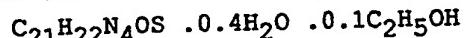
Found: C 69.52, H 6.09, N 15.35, S 9.05

5

Example 46

2-(2-Methylphenylamino)-4-(N-methyl-2-methylphenylamino)-
6-oxo-5,7-dihydrothieno[3,4-d]pyrimidine

10 A solution of m-chloroperbenzoic acid (0.61 g, 3.58 mmol) in dry dichloromethane (20 ml) was added dropwise to a stirred solution of 2-[(2-methylphenyl)amino]-4-(N-methyl-2-methylphenyl)amino-5,7-dihydrothieno[3,4-d]pyrimidine (1.0 g, 2.76 mmol) in dry dichloromethane (25 ml) at -35° to -40°C. The mixture was stirred for 1 hour at this temperature then allowed to stand overnight. Ammonia gas was bubbled through the solution for 5 min, then the deposited solid was filtered off, washed with dichloromethane and discarded. The combined filtrate was evaporated to dryness and the residual oil was purified by silica gel chromatography, eluted with CHCl₃. The product was obtained as an orange coloured solid; yield 0.38 g (38%), m.p. 100-105°C.



25 Calc: C 65.23, H 6.04, N 14.35, S 8.22

Found: C 64.90, H 5.85, N 14.39, S 8.41

Example 47

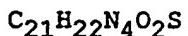
30 2-[(2-Methylphenylamino)-4-(N-methyl-2-methylphenylamino)-
6,6-dioxo-5,7-dihydrothieno[3,4-d]pyrimidine

- 61 -

A solution of m-chloroperbenzoic acid (3.56 g, 0.0207 mol) in dry dichloromethane (20 ml) was added dropwise with stirring to a solution of 2-[(2-methylphenyl)amino]-4-(N-methyl-2-methylphenyl)amino-5,7-

5 dihydrothieno[3,4-d]pyrimidine (2.5 g, 0.0069 mol) in dry dichloromethane (50 ml) at 25-30°C. The mixture was stirred at room temperature for 16 hours, ammonia gas bubbled through the solution for 10 min, and the deposited solid filtered off and discarded. The filtrate was

10 columned on silica gel, eluted with chloroform. A second column was required to obtain the product as a pale brown solid, m.p. 177-179°C.



Calc: C 63.94, H 5.62, N 14.20
15 Found: C 63.68, H 5.58, N 13.91

Example 48

2-(2-Methylphenylamino)-4-(N-methylphenylamino)-6,7-
20 dihydrothieno[3,2-d]pyrimidine

(i) 2-Thio-4-oxo-6,7-dihydrothieno[3,2-d]pyrimidine

25 2-Carbomethoxy-3-oxotetrahydrothiophene (55 g, 0.316 mol) was added to a solution of sodium (14.5 g, 0.632 mol) in ethanol (500 ml), followed by the addition of thiourea (24 g, 0.316 mol). The mixture was stirred for 24 hours at room temperature, then the solvent evaporated. The residual solid was dissolved in water, acidified
30 with glacial acetic acid and the deposited solid filtered off, washed with water, and dried; yield 25 g (42%).

(ii) 2-Methylthio-4-oxo-6,7-dihydrothieno[3,2-d]pyrimidine

- 62 -

2-Thio-4-oxo-6,7-dihydrothieno[3,2-d]pyrimidine (25 g, 0.134 mol) was added to a solution of sodium hydroxide (5.88 g, 0.147 mol) in water (50 ml) and ethanol (500 ml). Methyl iodide (20.8 g, 0.147 mol) was added, and the 5 mixture was stirred under reflux for 16 hours. After cooling, the solid was filtered off, washed with diethyl ether and dried; yield 19.5 g (69%), m.p. 265-270°C.

(iii) 2-[(2-Methylphenyl)amino]-4-oxo-6,7-
10 dihydrothieno[3,2-d]pyrimidine

A mixture of 2-methylthio-4-oxo-6,7-dihydrothieno-[3,2-d]pyrimidine (19.5 g, 0.0975 mol) and o-toluidine (80 ml, excess) was stirred and heated at 180-200°C for 16 15 hours. After cooling, the mixture was poured into diethyl ether (600 ml) and stirred for 30 min at room temperature, then the solid was filtered off, washed with ether and dried; yield 16.1 g (64%), m.p. 249-252°C.

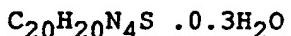
20 (iv) 2-[(2-Methylphenyl)amino]-4-chloro-6,7-
dihydrothieno[3,2-d]pyrimidine

2-[(2-Methylphenyl)amino]-4-oxo-6,7-dihydrothieno-[3,2-d]pyrimidine (11.0 g, 0.0424 mol) was mixed with 25 phosphoryl chloride (150 ml, excess) and stirred under reflux for 90 min. The excess acid chloride was removed by evaporation, the residual oil treated with ice/water and extracted with CHCl₃, then the extracts were washed with sat. NaHCO₃ and water, dried over MgSO₄ and the 30 solvent evaporated leaving an oil; yield 12.3 g (greater than theoretical), used without further purification.

(v) 2-[(2-Methylphenyl)amino]-4-(N-methylphenyl)amino]-
6,7-dihydrothieno[3,2-d]pyrimidine

- 63 -

2-[(2-Methylphenyl)amino]-4-chloro-6,7-dihydrothieno[3,2-d]pyrimidine (2.5 g, 9 mmol, crude) was mixed with N-methylaniline (9 ml, excess) and the mixture was stirred at 200°C for 2 hours. After cooling, the product was purified by silica gel chromatography, eluted with EtOAc/pet. ether (1:4). The title compound was obtained as a pale brown solid; yield 1.1 g (34%), m.p. 184-185°C.

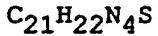


10 Calc: C 67.88, H 5.88, N 15.83, S 9.08
 Found: C 67.71, H 5.77, N 15.70, S 9.06

Example 49

15 2-(2-Methylphenylamino)-4-(N-methyl-2-methylphenylamino)-6,7-dihydrothieno[3,2-d]pyrimidine

A mixture of 2-[(2-Methylphenyl)amino]-4-chloro-6,7-dihydrothieno[3,2-d]pyrimidine (4.9 g, 0.0176 mol) and N-methyl-o-toluidine (15 ml, excess) was stirred at 200°C for 3 hours. After cooling, the crude oil was dissolved in CHCl₃ and the oil purified by silica gel chromatography, eluted with CHCl₃. A further column was required to obtain the product as a grey coloured solid, m.p. 162-165°C.



Calc: C 69.58, H 6.12, N 15.46
 Found: C 69.63, H 6.07, N 15.31

30 Example 50

2-(2-Methylphenylamino)-4-(N-methylphenylamino)-thiopyrano[4,3-d]pyrimidine hydrochloride

- 64 -

(i) 2-(Methylthio)thiopyrano[4,3-d]pyrimidin-4-one

To a solution of potassium hydroxide (1.08 g, 19 mmol) in methanol (25 ml) was added 3-carbometoxytetrahydro-
5 1,4-thiapyrone (2.0 g, 12 mmol) and S-methylisothiouronium sulphate (3.34 g, 12 mmol). After stirring at room
temperature for 2 hours, the solution was evaporated to low volume, poured into water (150 ml) and acidified to pH
4 with glacial acetic acid. The white solid which
10 precipitated was filtered off, washed with water and dried to give the title compound (0.81 g), m.p. 212°C.

(ii) 2-[(2-Methylphenyl)amino]thiopyrano[4,3-d]pyrimidin-4-one

15 A mixture of 2-(methylthio)thiopyrano[4,3-d]pyrimidin-4-one (18.0 g, 84 mmol) and o-toluidine (63 g, excess) was heated at 160°C for 17 hours. Excess toluidine was distilled off under reduced pressure, and the residue
20 boiled with ethanol to give a yellow solid. This was filtered off and washed with ether to give the title compound (15.6 g), m.p. 237-240°C.

(iii) 2-[(2-Methylphenyl)amino]-4-chlorothiopyrano-[4,3-d]pyrimidine

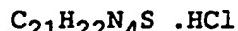
A mixture of 2-[(2-methylphenyl)amino]thiopyrano-[4,3-d]pyrimidin-4-one (13.46 g, 49 mmol) and phosphoryl chloride (40 ml, excess) was heated under reflux for 3 hours. The excess phosphoryl chloride was evaporated under reduced pressure, and the residue treated with ice-cold water, then extracted 3x with chloroform. The combined extracts were washed with aqueous sodium bicarbonate, water and brine, dried and evaporated to a dark red oil.

- 65 -

Chromatography (silica, CH₂Cl₂/MeOH) gave the title compound as a yellow oil (4.33 g).

(iv) 2-[(2-Methylphenyl)amino]-4-(N-methylphenylamino)-
5 thiopyrano[4,3-d]pyrimidine hydrochloride

A solution of 2-[(2-methylphenyl)amino]-4-chlorothiopyrano[4,3-d]pyrimidine (2.0 g, 6.9 mmol) and N-methylaniline (0.88 g, 8.2 mmol) in dioxan (60 ml) was 10 heated under reflux for 16 hours. The solvent was evaporated, and the residue crystallised from ethanol to yield the title compound (0.92 g), m.p. 225°C.



Found C 63.26, H 5.82, N 14.18, Cl 8.73
15 Requires C 63.22, H 5.81, N 14.04, Cl 8.89

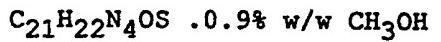
Example 51

2-(2-Methylphenylamino)-4-(N-methylphenylamino)6-
20 oxothiopyrano[4,3-d]pyrimidine

A solution of 2-[(2-methylphenyl)amino]-4-(N-methylphenylamino)thiopyrano[4,3-d]pyrimidine hydrochloride (2.0 g, 5 mmol) in dichloromethane was 25 washed with aqueous sodium bicarbonate then brine, dried over potassium carbonate, and the drying agent filtered off. The filtrate was cooled to -40°C, and a solution of m-chloroperbenzoic acid (1.12 g, 6.5 mmol) in dichloromethane added dropwise. After a further 0.75 h at 30 -40°C, the cooling bath was removed and ammonia gas passed through the solution for 5 min. The precipitate was filtered off on celite, and the filtrate evaporated to an

- 66 -

orange oil, which crystallised on trituration with ether.
Recrystallisation from chloroform/ethanol, then from
methanol, gave the title compound (0.75 g), m.p. 186°C.



5 Found C 66.05, H 5.88, N 14.69, S 8.75
Requires C 66.38, H 6.09, N 14.66, S 8.39

- 67 -

Biological Data.

(A) H⁺K⁺ATPase Activity.

5 The effects of a single high concentration (100 µM) of a compound of structure (I) on K-stimulated ATPase activity in lyophilised gastric vesicles was determined. Preferred compounds of structure (I) were also tested over a range of concentrations to determine IC₅₀ values.

10

(i) Preparation of lyophilised gastric vesicles (H/K-ATPase).

15 Lyophilised gastric vesicles were prepared from pig fundic mucosa after the method of Keeling et. al. (Biochem. Pharmacol., 34, 2967, 1985).

(ii) K⁺-stimulated ATPase activity.

20 K⁺-stimulated ATPase activity was determined at 37° in the presence of the following : 10 mM Pipes/Tris buffer pH 7.0, 2 mM MgSO₄, 1 mM KCl, 2 mM Na₂ATP and 3-6 µg protein/ml lyophilised gastric vesicles. After incubation for 30 minutes, the inorganic phosphate hydrolysed from 25 ATP was determined by the method of Yoda and Hokin (Biochem. Biophys. Res. Commun. 40, 880, 1970).

30 Compounds of structure (I) were dissolved in dimethylsulphoxide which up to the highest concentration used had no effect on K⁺-stimulated ATPase activity.

- 68 -

The effect of the highest concentration of each compound of structure (I) on the recovery of a standard amount of inorganic phosphate was also determined.

5 (iii) Results.

The compounds of the examples had IC₅₀ values of less than 50µM.

- 69 -

Example A

A tablet for oral administration is prepared by combining

| | Mg/Tablet |
|----------------------------|-----------|
| 5 | |
| Compound of structure (I) | 100 |
| lactose | 153 |
| Starch | 33 |
| 10 crospovidone | 12 |
| microcrystalline cellulose | 30 |
| magnesium stearate | 2 |
| | <hr/> |
| | 330 mg |
| | <hr/> |

15 into a 9 mm tablet.

Example B

20 An injection for parenteral administration is prepared from the following

%w:w

| | | |
|----|---------------------------|-------------|
| 25 | Compound of structure (I) | 0,50% (w:v) |
| | 1M citric acid | 30% (v:v) |
| | sodium hydroxide (qs) | to pH 3.2 |
| | water for injection EP | to 100 ml |

30 The compound of structure (I) is dissolved in the citric acid and the pH slowly adjusted to pH 3.2 with the sodium hydroxide solution. The solution was then made up to 100 ml with water, sterilised by filtration and sealed into appropriately sized ampoules and vials.

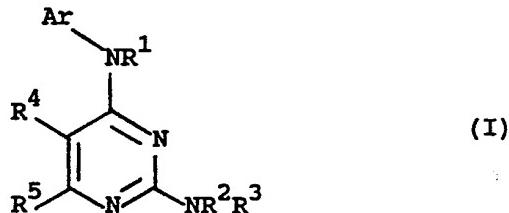
35

- 70 -

Claims.

1. A compound of structure (I)

5



10

in which

Ar is a phenyl ring which can be optionally substituted by
one to three groups selected from hydroxy, halogen,
15 CF₃, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkylthio, cyano,
amino, carbamoyl carboxy or C₁₋₄alkanoyl;

20 R¹ is hydrogen or C₁₋₄alkyl;
R² and R³ are the same or different and are each hydrogen,
C₁₋₄alkyl or Ar¹ where Ar¹ is as defined for Ar; or
R² and R³ together with the nitrogen atom to which
they are attached form a saturated or unsaturated
ring optionally containing one or more further
25 heteroatoms.

30 one of R⁴ and R⁵ is hydrogen or C₁₋₄alkyl; and the other
is hydrogen, C₁₋₄alkyl, hydroxyc₁₋₄alkyl,
C₁₋₄alkoxyC₁₋₄alkyl, amino, C₁₋₄alkanoyl,
C₁₋₄alkylthioc₁₋₄alkyl, Ar²(CH₂)_nOC₁₋₄alkyl,
in which Ar² is an optionally substituted phenyl ring
as defined for Ar and n is 0 to 4; or -(CH₂)_mAr³,
in which m is 1 to 4 and Ar³ is an optionally
substituted phenyl ring as defined for Ar; or R⁴ and

- 71 -

R^5 together with the carbon atoms to which they are attached form a 5- or 6-membered ring, optionally containing one or more heteroatoms;

5 or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 in which one of R^2 and R^3 is hydrogen and the other is an optionally substituted phenyl ring.

10

3. A compound according to claim 1 which is 5,6-dimethyl-2-[(2-methylphenyl)amino]-4-(N-methyl-2-methylphenyl amino)pyrimidine hydrochloride, 5,6-dimethyl-2-[(2-methylphenyl)amino]-4-(N-methyl-phenylamino)pyrimidine hydrochloride, 5-methyl-6-n-propyl-2-[(2-methylphenyl)amino]-4-(N-methylphenylamino) pyrimidine hydrochloride, 2-[(2-methylphenyl)amino]-4-(N-methyl-2-methylphenylamino)-5,6,7,8-tetrahydroquinazoline hydrochloride, or 2-(2-phenylamino)-4-(N-methylphenylamino)-5,6,7,8-tetrahydroquinazoline hydrochloride.

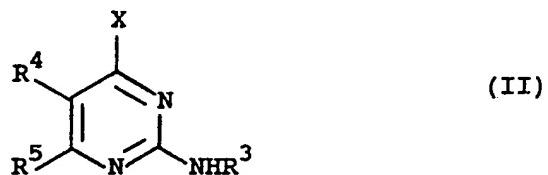
15

20

25

4. A process for preparing a compound according to claim 1 which comprises reaction of a compound of structure (II)

30



in which R^3 , R^4 and R^5 are as described for structure (I), and X is a group displaceable by an amine,

- 72 -

with an amine of structure ArNR¹H in which Ar and R¹ are as described for structure (I), and optionally thereafter, forming a pharmaceutically acceptable salt.

- 5 5. A pharmaceutical composition comprising a compound of structure (I) or a pharmaceutically acceptable salt thereof as described in claim 1 in association with a pharmaceutically acceptable carrier.
- 10 6. A compound of structure (I) for use in therapy.
7. A compound of structure (II) as described in claim 4.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 91/01007

| I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ | | | | | | | | | | | | | | | | | | | | | | | | | |
|--|---|---|--|--|------------------------|--|-------------------------------------|---|---|---------------|---------------|---|---|---|---|-------|---|--|-------|---|---|-----|--|--|-----|
| According to International Patent Classification (IPC) or to both National Classification and IPC | | | | | | | | | | | | | | | | | | | | | | | | | |
| Int.C1.5 C 07 D 239/48 C 07 D 239/50 C 07 D 239/42 A 61 K 31/505 C 07 D 239/95 C 07 D 495/04 C 07 D 239/70 | | | | | | | | | | | | | | | | | | | | | | | | | |
| II. FIELDS SEARCHED | | | | | | | | | | | | | | | | | | | | | | | | | |
| Minimum Documentation Searched ⁷ | | | | | | | | | | | | | | | | | | | | | | | | | |
| <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 25%;">Classification System</th> <th colspan="3" style="width: 75%;">Classification Symbols</th> </tr> </thead> <tbody> <tr> <td style="width: 25%;">Int.C1.5</td> <td style="width: 25%;">C 07 D 239/00</td> <td style="width: 25%;">C 07 D 495/04</td> <td style="width: 25%;"></td> </tr> </tbody> </table> | | | | | Classification System | Classification Symbols | | | Int.C1.5 | C 07 D 239/00 | C 07 D 495/04 | | | | | | | | | | | | | | |
| Classification System | Classification Symbols | | | | | | | | | | | | | | | | | | | | | | | | |
| Int.C1.5 | C 07 D 239/00 | C 07 D 495/04 | | | | | | | | | | | | | | | | | | | | | | | |
| Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸ | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | |
| III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹ | | | | | | | | | | | | | | | | | | | | | | | | | |
| <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%;">Category¹⁰</th> <th style="width: 60%;">Citation of Document,¹¹ with indication, where appropriate, of the relevant passages¹²</th> <th style="width: 30%;">Relevant to Claim No.¹³</th> </tr> </thead> <tbody> <tr> <td>X</td> <td>GB,A,1229413 (I.C.I.) 21 April 1971, see pages 1,2(I,1),7,16,17 ---</td> <td>1,2,4,7</td> </tr> <tr> <td>X</td> <td>GB,A, 584917 (PARKE, DAVIS & CO.) 27 January 1947, see pages 1,6 (examples 7,8) ---</td> <td>1</td> </tr> <tr> <td>X</td> <td>US,A,3478030 (J.H. SHORT) 11 November 1969, see columns 1-3 ---</td> <td>1,4-7</td> </tr> <tr> <td>X</td> <td>US,A,2748124 (R.R. BURTNER) 29 May 1956, see columns 1-4 ---</td> <td>1,4,7</td> </tr> <tr> <td>X</td> <td>JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 21, July-August 1984, (US), H. GERSHON et al.: "Pyrimidines. 7. A Study of the chlorination of pyrimidines with phosphorus oxychloride in the presence of N,N-dimethylaniline", pages 1161-1167, see pages 1162-1166 ----</td> <td>1-7</td> </tr> <tr> <td></td> <td></td> <td>-/-</td> </tr> </tbody> </table> | | | | | Category ¹⁰ | Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹² | Relevant to Claim No. ¹³ | X | GB,A,1229413 (I.C.I.) 21 April 1971, see pages 1,2(I,1),7,16,17 --- | 1,2,4,7 | X | GB,A, 584917 (PARKE, DAVIS & CO.) 27 January 1947, see pages 1,6 (examples 7,8) --- | 1 | X | US,A,3478030 (J.H. SHORT) 11 November 1969, see columns 1-3 --- | 1,4-7 | X | US,A,2748124 (R.R. BURTNER) 29 May 1956, see columns 1-4 --- | 1,4,7 | X | JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 21, July-August 1984, (US), H. GERSHON et al.: "Pyrimidines. 7. A Study of the chlorination of pyrimidines with phosphorus oxychloride in the presence of N,N-dimethylaniline", pages 1161-1167, see pages 1162-1166 ---- | 1-7 | | | -/- |
| Category ¹⁰ | Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹² | Relevant to Claim No. ¹³ | | | | | | | | | | | | | | | | | | | | | | | |
| X | GB,A,1229413 (I.C.I.) 21 April 1971, see pages 1,2(I,1),7,16,17 --- | 1,2,4,7 | | | | | | | | | | | | | | | | | | | | | | | |
| X | GB,A, 584917 (PARKE, DAVIS & CO.) 27 January 1947, see pages 1,6 (examples 7,8) --- | 1 | | | | | | | | | | | | | | | | | | | | | | | |
| X | US,A,3478030 (J.H. SHORT) 11 November 1969, see columns 1-3 --- | 1,4-7 | | | | | | | | | | | | | | | | | | | | | | | |
| X | US,A,2748124 (R.R. BURTNER) 29 May 1956, see columns 1-4 --- | 1,4,7 | | | | | | | | | | | | | | | | | | | | | | | |
| X | JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 21, July-August 1984, (US), H. GERSHON et al.: "Pyrimidines. 7. A Study of the chlorination of pyrimidines with phosphorus oxychloride in the presence of N,N-dimethylaniline", pages 1161-1167, see pages 1162-1166 ---- | 1-7 | | | | | | | | | | | | | | | | | | | | | | | |
| | | -/- | | | | | | | | | | | | | | | | | | | | | | | |
| * Special categories of cited documents : ¹⁰ "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed | | | | | | | | | | | | | | | | | | | | | | | | | |
| "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family | | | | | | | | | | | | | | | | | | | | | | | | | |
| IV. CERTIFICATION | | | | | | | | | | | | | | | | | | | | | | | | | |
| Date of the Actual Completion of the International Search | | Date of Mailing of this International Search Report | | | | | | | | | | | | | | | | | | | | | | | |
| 19-08-1991 | | 13 OCT 1991 | | | | | | | | | | | | | | | | | | | | | | | |
| International Searching Authority EUROPEAN PATENT OFFICE | | Signature of Authorized Officer MISS D. S. KOWALCZYK | | | | | | | | | | | | | | | | | | | | | | | |

| III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET) | | |
|--|---|-----------------------|
| Category | Citation of Document, with indication, where appropriate, of the relevant passages | Relevant to Claim No. |
| X | JOURNAL OF MEDICINAL CHEMISTRY, vol. 11, 1968, (Washington, US), G.J. ATWELL et al.: "Potential antitumor agents. VIII. Bisquaternary salts", pages 690-694, see pages 691-692 --- | 1 |
| X | CHEMICAL ABSTRACTS, vol. 71, 1969, page 295, abstract no. 30453h, (Columbus, Ohio, US), E.A. ARUTYUNYAN et al.: "Direct amination of uracils and related compounds", & IZV. AKAD. NAUK SSSR, SER. KHIM. 1969, (3), 655-62, see the abstract --- | 1,2 |
| X | CHEMICAL ABSTRACTS, vol. 93, 1980, pages 925-926, abstract no. 46582q, (Columbus, Ohio, US), A.V. IVASHCHENKO et al.: "Synthesis and study of derivatives of 2,4-diamino- and 2-amino-4-(1H-pyrazol-1-yl)pyrimidine", & KHIM. GETEROTSIKL. SOEDIN. 1980, (3), 404-7, see the abstract --- | 1,2 |
| X | CHEMICAL ABSTRACTS, vol. 95, 1981, page 648, abstract no. 97712f, (Columbus, Ohio, US), D. GHOSH: "2,4-Bis(aryl amino)-6-methylpyrimidines as antimicrobial agents", & J. INDIAN CHEM. SOC. 1981, 58(5), 512-13, see the abstract --- | 1,2,5,6 |
| X | CHEMICAL ABSTRACTS, vol. 108, 1988, page 724, abstract no. 56043g, (Columbus, Ohio, US), K.M. GHONEIM et al.: "Synthesis and evaluation of some 2-, 4- and 2,4-di-substituted-6-methylpyrimidine derivatives for antimicrobial activity", & J. INDIAN CHEM. SOC. 1986, 63(10), 914-17, see the abstract --- | 1,2,4,6 |
| X | CHEMICAL ABSTRACTS, vol. 108, 1988, page 670, abstract no. 204585c, (Columbus, Ohio, US), K.M. GHONEIM et al.: "Synthesis and evaluation of some 2-, 4-, and 2,4-disubstituted-6-methylpyrimidine derivatives for antimicrobial activity", & EGYPT. J. PHARM. SCI. 1987, 28(1-4), 117-26, see the abstract --- | 1-7 |
| X | CHEMICAL ABSTRACTS, vol. 114, 1991, page 684, abstract no. 62037y, (Columbus, Ohio, US), K.M. GHONEIM et al.: "Synthesis of some Mannich bases of 2- and 4-amino- and 2,4-diamino-6-methylpyrimidines as potential biodynamic agents", & EGYPT. J. CHEM. 1987, (PUB. 1989), 30(6), 295-304, see the abstract --- | 1,5 |

| III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET) | | |
|--|---|-----------------------|
| Category | Citation of Document, with indication, where appropriate, of the relevant passages | Relevant to Claim No. |
| X | CHEMICAL ABSTRACTS, vol. 66, 1967, page 2735, abstract no. 28731a, (Columbus, Ohio, US), C.A.R. HURT et al.: "The synthesis of pyrimidoquinazolones", & TETRAHEDRON SUPPL. NO. 7, 227-32(1966), see the abstract --- | 1 |
| A | EP,A,0322133 (SMITHKLINE) 28 June 1989, see pages 1-4, claims --- | 1,3-7 |
| P,X | WO,A,9012790 (I.C.I.) 1 November 1990, see pages 24-44,51-76 --- | 1-3,7 |
| P,X | EP,A,0404356 (SMITHKLINE) 27 December 1990, see the whole document ----- | 1,4-7 |

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. EP 9101007
SA 48029

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 20/09/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|--|------------------|-------------------------|---------|------------------|
| GB-A- 1229413 | 21-04-71 | DE-A- | 1770637 | 05-01-72 |
| | | FR-A- | 1572620 | 27-06-69 |
| | | NL-A- | 6808306 | 16-12-68 |
| | | US-A- | 3670077 | 13-06-72 |
| GB-A- 584917 | | None | | |
| US-A- 3478030 | 11-11-69 | None | | |
| US-A- 2748124 | | None | | |
| EP-A- 0322133 | 28-06-89 | AU-A- | 2823089 | 05-07-89 |
| | | CN-A- | 1033380 | 14-06-89 |
| | | WO-A- | 8905297 | 15-06-89 |
| | | JP-T- | 2502462 | 09-08-90 |
| WO-A- 9012790 | 01-11-90 | AU-A- | 5435490 | 16-11-90 |
| | | CN-A- | 1047080 | 21-11-90 |
| | | EP-A- | 0422178 | 17-04-91 |
| | | GB-A- | 2230527 | 24-10-90 |
| EP-A- 0404356 | 27-12-90 | JP-A- | 3017083 | 25-01-91 |

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82